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Award Number: DAMD17-96-C-6069

TITLE: Breast Cancer Center Support Contract

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CONTRACTING ORGANIZATION: Georgetown University
Washington, DC 20057

REPORT DATE: March 2001

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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20010620 140

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE March 2001	3. REPORT TYPE AND DATES COVERED Final (1 Sep 96 - 31 Jan 01)		
4. TITLE AND SUBTITLE Breast Cancer Center Support Contract		5. FUNDING NUMBERS DAMD17-96-C-6069		
6. AUTHOR(S) Kevin J. Cullen, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Georgetown University Washington, DC 20057 E-Mail: cullenk@gunet.georgetown.edu		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) This document represents the final report for our Breast Cancer Center Support Grant. Our grant consisted of five areas, three projects and two cores. Projects included: Project 1 - Impact of Genetic Testing for Breast Cancer Susceptibility; Project 2 - A Coordinated Approach to Breast Cancer Diagnosis; and Project 3 - Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer. These projects were supported by Core 1 - Patient Accession Core, and Core 2 - Cancer Clinical and Economic Outcomes Evaluations Core. During the project period, each of the cores were fully functional, and each of the projects met its stated objectives. Detailed summaries of the work completed is provided for each of the project areas. Taken together, we believe that these projects, supported by their appropriate cores, have been successful in meeting their statements of work, and in fulfilling their scientific objectives during the granting period.				
14. SUBJECT TERMS Breast Cancer			15. NUMBER OF PAGES 744	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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PRINCIPAL INVESTIGATOR'S INTRODUCTION

Since the inception of our Breast Cancer Center Grant in 1996, the project leaders and core directors have worked closely with one another to achieve the goals of the grant. As described within our final report, **Project 1 (Impact of Genetic Testing For Breast Cancer Susceptibility)** provided data which were the first to document predictors of uptake in a high-risk clinically-based population. These results suggest that cancer worries may motivate testing use, and that a woman's coping style may affect her anticipatory reactions to testing. **Project 2 (A Coordinated Approach to Breast Cancer Diagnosis)** has completed its accrual The overall goals of **Project 3 (Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer)** were to evaluate the effects of angiogenic inhibitors in prospective clinical trials in breast cancer patients. We have successfully completed a randomized phase I/II study of thalidomide, which provided insights into the relative lack of activity of high dose (800-1200 mg) and standard dose (200 mg) thalidomide. We also completed a Phase I trial that provided additional information regarding our proposal to conduct a randomized trial to determine whether TNP-470 contributes added benefit to the chemotherapeutic agent, paclitaxel. Although thus far we have failed to observe apparent efficacy benefit with these strategies, these data are of critical importance to the research community.

Outstanding efforts have also been demonstrated by the two cores support by this award. Based on an analysis of **Core 1 (Patient Accession Core)** experience, and a review of other successful and unsuccessful efforts at minority clinical trials accrual, the Lombardi Cancer Center (LCC) proposed to expand minority accrual to breast cancer research trials. We expanded the existing network of oncology office practices, and their affiliated internist, ob/gyn and surgical practices. We were less successful than hoped in sustaining these collaborations, and therefore refocused our efforts to provide web-based infrastructure for clinical trials information, to expand the standard clinical trials' information base, in hopes to ultimately enhance accrual. **Core 2 (Cancer Clinical and Economic Outcomes Evaluation Core)** extended the state-of-the-art science of conducting outcomes research by composing a unique cross-disciplinary research team with the methodological expertise to evaluate the costs and benefits of new and existing cancer services. Detailed information about each of the projects, and the two cores which support them, is provided on the following pages.

PROJECT 1: IMPACT OF GENETIC TESTING FOR BREAST CANCER SUSCEPTIBILITY

I. INTRODUCTION: Up to 10% of breast/ovarian cases are due to an alteration in the BRCA1 or BRCA2 genes. Women who have an alteration in either of these genes have an estimated 55-85% risk of developing breast cancer and a 15-60% chance of getting ovarian cancer. Other cancers also occur with increased frequency in gene carriers, such prostate cancer. First-degree relatives of individuals with a BRCA1 or BRCA2 mutation have a 50% chance of carrying the altered gene. Thus, men may also derive clinically significant information from genetic testing for themselves and their family members.

This study is designed to gather data on the determinants of testing uptake, as well as the medical and psychological implications of genetic counseling and testing. We are also interested in learning about individuals who decline such counseling and testing and how this choice impacts their well-being and medical decision-making. (Note: For brevity, this program is referred to as CARE, Cancer Assessment and Risk Evaluation.) The specific aims of this project are as follows:

- 1) to identify determinants of who decides to undergo BRCA1/2 testing;
- 2) to evaluate the short- and long-term impact of BRCA1/2 testing on quality of life;
- 3) to evaluate the impact of genetic testing on prevention and surveillance practices;
- 4) to identify early predictors of psychological morbidity and nonadherence among participants in genetic testing programs; and
- 5) to develop a preliminary model to estimate the costs of BRCA1/2 testing per quality-adjusted life years ahead.

II. BODY

A. Accrual, BRCA1/2 Testing Uptake, and Follow-Up

1. Major sources of recruitment and referral to the program continued to be from internal providers at Georgetown (e.g., medical oncologists and surgeons), relatives of individuals who test positive, and external providers within the DC metro area.
2. The final accrual figures are as follows: 889 individuals completed the initial baseline phone interview. Approximately 92% of the individuals who completed baselines are Caucasian and 8% are minorities. Of note, 726 individuals (82%) participated in a pre-test genetic counseling session.
3. Of the 726 individuals who completed an initial genetic counseling session, 639 (88%) chose to get tested and receive their results. Result outcomes are summarized below:
 - BRCA 1/2 Positive - **188**
 - BRCA 1/2 Mutation Negative or Ambiguous - **350**
 - BRCA 1/2 True Negative - **101**

4. Individuals were asked to participate in follow-up interviews regardless of whether they had genetic counseling or testing. Of those who did a baseline interview, 651 (73%) completed the 1 month follow-up interview; 599 completed the 6 month interview; and 535 completed the final 12 month interview. A final status for all individuals completing a baseline interview has been obtained (i.e., follow-up completed or subject was withdrawn by his/her request or could not be reached).

B. Preliminary model on the cost-effectiveness of counseling and testing for BRCA1/2 susceptibility mutations in high risk women.

A detailed report of this aim can be found in the report for Core 2: The Cancer Clinical and Economic Outcomes Core.

1. Costs: A large portion of the costs in the cost-effectiveness analysis of counseling and testing for BRCA1/2 susceptibility mutations are the costs of providing genetic counseling and testing. Dr. Lawrence and co-investigators performed a cost analysis of providing counseling and full gene sequencing to women at risk. To do this, we performed a time-motion study to determine counselor time costs to provide counseling and disclosure. Study participants were surveyed to determine travel time and need for dependent care during counseling. The test cost was calculated using the charge for full BRCA1/2 gene sequencing (Myriad Genetics, Inc.) multiplied by a Medicare-based cost-to-charge ratio. Counselors spent 4.2 hours per woman providing counseling. Counseling without testing cost \$213, while counseling, testing, and disclosure of results totaled \$2057. Counseling costs comprised only 16% of the total costs; thus, alternatives to full genetic counseling are unlikely to have a large impact on the overall cost of counseling and testing.

2. Quality of Life: We measure cost-effectiveness in this study in units of dollars per quality-adjusted life-years (QALYs) saved. To express outcomes in QALYs, we incorporate both survival and health utilities, or participants' preferences for the health outcomes of interest. We surveyed women participating in the CARE program to determine their utility for their own health and hypothetical health states of having breast or ovarian cancer using a linear rating scale (LRS) assessment. The mean utility for having a mastectomy for local breast cancer was .81 (on a scale where 0 represents death and 1.0 represents excellent health), although the utility for having metastatic disease was much lower at 0.49. Participants affected by breast cancer on average gave higher ratings than women not affected by breast cancer to local breast cancer health states. A detailed report can be found in the Core 2 report.

3. Cost-effectiveness: We used a computer simulation model to determine the long-term costs and outcomes of counseling and BRCA1/2 testing, simulating a cohort of high-risk women who either undergo counseling and testing, counseling alone, or no counseling and testing. The cost-effectiveness model would suggest that counseling and testing to women at similar level of risk as those in the CARE cohort improves outcomes, compared to not providing these services, at an

acceptable cost. The results are sensitive to the probability of the mutations in the women tested, and to what management options women choose if they are found to have a susceptibility mutation. Detailed results are included in the Core #2 report.

III. KEY RESEARCH ACCOMPLISHMENTS

- Uptake: The high rates of uptake of both genetic counseling and testing in our study are higher than most published estimates. It is likely that the fact that these services were offered at no cost was an incentive to participation as commercial costs for testing may be as much as \$2,580. In addition, participants were very concerned about the possibility of genetic discrimination; however, this research program offered several provisions to protect confidentiality.
- Predictors of uptake: These data are the first to document predictors of uptake in a high-risk clinically based population. For example, among breast cancer survivors, those who perceived their risk for ovarian cancer to be high were most likely to be tested, while those with high levels of spiritual faith were less likely to get tested. In addition to the importance of investigating these findings in future studies, these are issues that may be raised in the context of genetic counseling. (Schwartz et al., 2000)
- Baseline screening for breast and ovarian cancer: Breast and ovarian screening uptake in healthy women from hereditary breast cancer families is suboptimal, even for women over age 50, for whom annual mammography is clearly indicated. Having at least 1 relative with ovarian cancer was very strongly associated with ovarian cancer screening. Perceived and objective cancer risks were also independent predictors of uptake for CA-125 and ultrasound. No association between cancer worries/distress and either breast or ovarian cancer screening was found. Health care providers and patients need to be better informed about screening recommendations for high risk women, and the fact that women with a strong family history of breast cancer may also be at-risk for ovarian cancer. Follow-up of women will determine if genetic counseling/testing had an impact on screening behaviors. (Isaacs et al., in preparation)
- Impact: We found no evidence for adverse effects on perceived risk, cancer-related distress, or global distress in our cohort of high-risk women (i.e., affected probands and unaffected relatives) followed for six months post-counseling. Psychological benefits, reflected in decreases in cancer-related distress, were observed among unaffected relatives. This study is the first large clinic-based prospective analysis confirming the absence of psychological sequelae of BRCA1/2 testing in most participants. We did, however, observe modestly elevated distress levels in those who received positive or uninformative results. Therefore, these individuals may benefit from continued support. (Schwartz et al., manuscript in preparation for JNCI). In addition, we found that prior to BRCA1/2 test result disclosure, women's levels of psychological distress varied depending upon their coping style, although this was not true immediately after results were disclosed. At that time, carriers experienced significantly more distress than noncarriers, and effect which was not

modified by coping style. This information suggests certain assessments and interventions based on individual coping style may need to be utilized or developed for use prior to and following the receipt of test results. (Tercyak et al., Health Psychology, in press)

- **Cost:** The costs for genetic counseling are low relative to the costs involved in BRCA1/2 testing. Thus, findings derived from cost analyses in this research setting suggest that, in clinical practice, replacement of comprehensive genetic counselor counseling with a shorter time of physician counseling would not significantly lower overall costs.

IV. REPORTABLE OUTCOMES

A. Manuscripts and Abstracts from Project Data

1) Peer-reviewed publications/commentaries

Brunet JS, Ghadirian P, Rebbeck TR, Lerman C, Garber JE, Tonin PN, Abrahamson J, Foulkes WD, Daly M, Wagner-Costalas J, Godwin A, Olopade OI, Moslehi R, Liede A, Futreal PA, Weber BL, Lenoir GM, Lynch HT, Narod SA. Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. Journal of the National Cancer Institute 1998; 90(10):761-766.

Frank TS, Manley SA, Olopade OI, Cummings S, Garber JE, Bernhardt B, Antman K, Russo D, Wood ME, Mullineau L, Isaacs C, Peshkin B, Buys S, Venne V, Rowley PT, Loader S, Offit K, Robson M, Hampel H, Brenner D, Winer EP, Clark S, Weber B, Strong LC, Rieger P, McClure M, Ward BE, Shattuck-Eidens D, Oliphant A, Skolnick, Thomas A. Sequence analysis of BRCA1 and BRCA2: Correlation of mutations with family history and ovarian cancer risk. Journal of Clinical Oncology 1998; 16:2417-2425.

Jernstrom H, Lerman C, Ghadirian P, Lynch H, Weber B, Garber J, Daly M, Olopade OI, Foulkes WD, Warner E, Brunet JS, Narod SA. Pregnancy increases the risk of early breast cancer in BRCA1 and BRCA2 carriers. Lancet 1999; 354:1846-1850.

Lerman C, Peshkin BN, Hughes C, Isaacs C. Family disclosure in genetic testing for cancer susceptibility: determinants and consequences. Journal of Health Care Law and Policy 1998; 1(2):353-372.

Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, Brunet JS, Ponder BAJ for the Hereditary Ovarian Cancer Clinical Study Group*. Oral contraceptives and the risk of hereditary ovarian cancer. New England Journal of Medicine 1998; 339:424-428. (*Including C. Lerman and B. Peshkin from Georgetown)

Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, Stoppa-Lyonnet D, Lerman C, Pasini B, de los Rios P, Weber B, Lynch H, for the Hereditary Breast Cancer Clinical Study Group. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet 2000; 356:1876-1881.

Peshkin BN, Lerman C. Genetic counseling for hereditary breast cancer. Lancet 1999; 353:2176-2177.

Rebbeck TR, Levin AM, Eisen A, Snyder C, Watson P, Cannon-Albright L, Isaacs C, Olopade O, Garber JE, Godwin AK, Daly MB, Narod SA, Neuhausen SL, Lynch HT, Weber BL. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. Journal of the National Cancer Institute 1999; 91:475-479.

Schwartz MD, Hughes C, Roth J, Main D, Peshkin BN, Isaacs C, Kavanagh C, Lerman C. Spiritual faith and genetic testing decisions among high-risk breast cancer probands. Cancer Epidemiology Biomarkers and Prevention 2000; 9: 381-385.

Shattuck-Eidens D, Oliphant A, McClure M, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, Pruss D, Tavtigian SV, Teng DHF, Adey N, Staebell M, Gumpfer K, Lundstrom R, Hulick M, Kelly M, Holmen J, Lingenfelter B, Manley S, Fujimura F, Luce M, Ward B, Cannon-Albright L, Steele L, Offit K, Gilewski T, Norton L, Brown K, Schulz C, Hampel H, Schluger A, Giulotto E, Zoli W, Ravaoli A, Nevanlinna H, Pyrhonen S, Rowley P, Loader S, Osborne MP, Daly M, Tepler I, Weinstein PL, Scalia JL, Michaelson R, Scott RJ, Radice P, Pierotti MA, Garber JE, Isaacs C, Peshkin B, Lippman ME, Dosik MH, Caligo MA, Greenstein RM, Pilarski R, Weber B, Burgemeister R, Frank TS, Skolnick MH, Thomas A. BRCA1 sequence analysis in women at high risk for susceptibility mutations: risk factor analysis and implications for genetic testing. Journal of the American Medical Association 1997; 278:1242-1250.

Tercyak KP, Lerman C, Peshkin BN, Hughes C, Main D, Isaacs C, Schwartz MD. Effects of coping style and test result on anxiety among women participating in genetic counseling and testing for breast/ovarian cancer risk. Health Psychology (in press).

Tonin P, Weber B,Y, Offit K, Couch F, Rebbeck TR, Neuhauses S, Godwin AK, Daly M, Wagner-Costalos J, Berman D, Grana G, Fox E, Kane MF, Kolodner RD, Krainer M, Haber DA, Struwing JP, Warner E, Rosen B, Lerman C, Peshkin B, Norton L, Serova O, Foulkes WD, Lynch HT, Lenoir GM, Narod SA, Garber JE. Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. Nature Medicine 1996; 2(11):1179-1183.

Wang-Gohrke S, Weikel W, Risch H, Vesprini D, Abrahamson J, Lerman C, Godwin A, Moslehi R, Olipade O, Brunet JS, Stickeler E, Kieback DG, Kreienberg R, Weber B, Narod SA, Runnebaum IB. Intron variants of the p53 gene are associated with increased risk for ovarian cancer but not in carriers of BRCA1 or BRCA2 germline mutations. British Journal of Cancer 1999; 81:179-183.

2) Manuscripts under review or in progress

Berry DA, Iversen ES Jr, Gudbjartsson DF, Hiller E, Garber J, Peshkin BN, Lerman C, Watson P, Lynch H, Hilsenbeck S, Rubinstein WS, Hughes K, Parmigiani G. BRCAPRO validation, sensitivity of genetic testing of BRCA1 and BRCA2, and prevalence of other breast cancer susceptibility genes. Manuscript in preparation.

DeMarco TA, Peshkin BN, Brogan BM. Genetic counseling for breast and ovarian cancer susceptibility: closing the gap. Manuscript being revised for submission to the Journal of Genetic Counseling.

Isaacs C, Peshkin BN, Schwartz M, DeMarco TA, Main D, Lerman C. Breast and ovarian cancer screening practices in healthy women with a strong family history of breast or ovarian cancer. Manuscript in preparation.

Lawrence WF, Peshkin BN, Liang W, Isaacs C, Lerman C, Mandelblatt JS. Cost of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations. Cancer Epidemiology Biomarkers and Prevention, (under revision).

Peshkin BN, DeMarco TA, Brogan BM, Lerman C, Isaacs C. BRCA1/2 testing: complex themes in result interpretation. Revised manuscript under review at Journal of Clinical Oncology.

Schwartz MD, et al (authorship to be determined). The impact of BRCA1/BRCA2 mutation testing on psychological distress in a clinic-based sample. Manuscript in preparation for Journal of the National Cancer Institute.

3) Abstracts

Chittenden A, Wonderlick A, Peshkin B, Patenaude A, Garber J. BRCA1 testing in a transsexual male. Journal of Genetic Counseling 1999; 8:379 (abstract).

Eisen A, Rebbeck TR, Lynch HT, Lerman C, Ghadirian P, Dube MP, Weber BL, Narod SA. Reduction in breast cancer risk following bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers. American Journal of Human Genetics 2000; 67(2)Supp:250 (abstract).

Ganguly T, Citron M, Stott J, Isaacs C, Peshkin B, Godmilow L, Weber B, Ganguly A. Novel BRCA mutations in African American individuals with breast and ovarian cancer. American Journal of Human Genetics 1998; 63(4)Supp:366 (abstract).

Isaacs C, Peshkin B, Benkendorf J, Hughes C, Lerman C. Interest in testing for BRCA1: correlation between patient risk and desire for testing. Proceedings of the American Society of Clinical Oncology 1996; 15:329 (abstract).

Isaacs C, Peshkin B, Reutenauer J, Reed M, Main D, Lerman C. Cancer screening practices in women from high risk breast cancer families. Proceedings of the American Society of Clinical Oncology 1997; 17:1916 (abstract).

Peshkin BN, Lerman C, Isaacs C, Brown KM, de Leon A, Abbaszadegan MR. A detection panel of prevalent mutations in BRCA1/2 genes is sensitive and cost effective in an initial screen of high risk patients. Proceedings of the American Association of Cancer Research 1998; 39:3232 (abstract).

Peshkin BN, DeMarco T, Brogan B, Lerman C, Isaacs C. BRCA1/2 testing: complex themes in result interpretation. Proceedings of the American Society of Clinical Oncology 2000; 19: 2632A (abstract).

Weber BL, Punzalan C, Eisen A, Lynch HT, Narod SA, Garber JE, Isaacs C, Daly MB, Neuhausen SL, Rebbeck TR. Ovarian cancer risk reduction after bilateral prophylactic oophorectomy (BPO) in BRCA1 and BRCA2 mutation carriers. American Journal of Human Genetics 2000; 67(2)Supp:251 (abstract).

4) Book chapters

Benkendorf JL, Peshkin BN, Lerman C. Impact of genetic information and genetic counseling on public health. In: Khoury MJ, Burke W, Thomson EJ, eds. Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease. New York: Oxford University Press, 2000: pages 361-383.

Isaacs CJD, Peshkin BN. Hereditary breast cancer: an overview. In: Hortobagyi GN, Khayat D, eds. Progress in Anti-cancer Chemotherapy. Paris, France: Springer-Verlag, 1999: pages 57-80.

Isaacs C, Peshkin BN, Lerman C. Evaluation and management of women with a strong family history of breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK (eds.), Diseases of the Breast (2nd edition). Philadelphia, PA: J.B. Lippincott, 2000: pages 237-254.

Lerman C, Peshkin BN. Psychosocial issues in BRCA1/2 testing. In: Bowcock AM (ed.), Breast Cancer: Molecular Genetics, Pathogenesis, and Therapeutics (Contemporary Cancer Research series). NJ: Humana Press, 1999: pages 247-266.

A. Other Reportable Outcomes

1. Registry development. Participants in the CARE program are invited to contribute to our Familial Cancer Registry. This registry is a repository for blood and tumor DNA, as well as pathology information. A database containing risk factor information has also been developed. Data from CARE participants, combined with data from several other sites, has been used to determine the effects of oral contraceptives, cigarette smoking, parity, tamoxifen, prophylactic surgery, and other factors on cancer risks in mutation carriers (see publication list).
2. Funding applied for based on this work. Based in part from preliminary data on this work and the "standard genetic counseling" protocols refined through this grant, funding for additional studies has been awarded. For example, Chanita Hughes, PhD is the Principal Investigator for a new DOD funded study, "Genetic Counseling for Breast Cancer Susceptibility in African American Women." This is a randomized study of a culturally tailored genetic counseling protocol, modified from the one used for the current study. Dr. Hughes is also the PI for an NIH supported study, "Comparing Models of Counseling for BRCA1/2 Testing." This randomized study is evaluating the impact of psychosocial telephone counseling versus standard genetic counseling in female mutation carriers. Once that study completes accrual, Marc Schwartz, PhD will begin recruitment for his study

funded by NIH, "Interactive Decision-Aid for BRCA1/2 Mutation Carriers." This is also a randomized study evaluating the impact of a CD-ROM-based intervention versus standard genetic counseling on decisions about breast cancer screening and prevention, and quality of life in female mutation carriers.

High-risk individuals ascertained through the CARE program may also be invited into the NIH funded "Cancer Genetics Network." This is a grant to develop an infrastructure of nationwide resources that will enable researchers to have access to interested participants for cancer genetics studies. In addition, a subcontract was recently awarded by NIH to study the efficacy of prophylactic mastectomy and oophorectomy in mutation carriers, for which Claudine Isaacs, MD is the principal investigator.

3. Training supported by this award. Since 1998, six genetic counseling students from three accredited master's level training programs (National Human Genome Research Institute, University of Michigan, and Howard University) completed clinical rotations at Georgetown University. Under the close supervision of the genetic counselors, these individuals had an opportunity to observe and take part in the genetic counseling of research participants.

V. CONCLUSIONS

- Our findings show that a majority of individuals who complete an initial baseline telephone interview opt to participate in genetic counseling and testing. Prior to genetic counseling, the degree of adherence to breast and ovarian cancer screening recommendations is low, and it remains to be seen whether genetic counseling/testing impacts these practices. There do not appear to be significant adverse psychological effects as a result of participation in genetic counseling and testing, even among those who test positive. However, a woman's coping style may affect her anticipatory reactions to testing.
- Genetic counseling for hereditary breast/ovarian cancer is complex. Although the interpretation of most results is straightforward, it is not infrequent that uninformative or ambiguous results will be obtained. Among those who test positive, it is critical to help participants understand and assimilate the limitations in the current state of knowledge (e.g., uncertainty about cancer risks and efficacy of screening/prevention options). However, even in this context, facilitation of medical decision-making, family communication, and personal coping is important through the genetic counseling process. Future studies by our group are examining adjuncts to standard genetic counseling such as psychosocial telephone counseling and a CD-ROM decision-aid.
- Important epidemiologic data from our participants combined with those from other centers have been instrumental in the study of risk modifiers in mutation carriers.
- Data obtained from this study have also been used to estimate the costs of providing genetic counseling and testing, which may be useful in clinical practice.
- We are continuing to evaluate the decision-making patterns of participants with respect to longer-term psychological and medical outcomes, as well as patterns and predictors of family

disclosure. In addition, through the registry and other funded projects, we hope to gain a better understanding of the genetic epidemiology of hereditary breast cancer and the efficacy of prevention strategies.

- Now that follow-up has been completed, further data analysis will determine adherence to screening recommendations, uptake of prophylactic surgery, and psychosocial outcomes over a one-year period.

VI. REFERENCES -- none additional

VII. APPENDICES

- CARE educational materials and Article reprints
- Selected abstracts of unpublished papers

PROJECT 2: A COORDINATED APPROACH TO BREAST CANCER DIAGNOSIS

I. INTRODUCTION: This project focused on developing improved paradigms for breast cancer diagnosis using new methods of imaging and molecular markers of neoplasia measured in nipple aspirate fluid. The ultimate objective of such research was to reduce the number of unnecessary biopsies by improving the specificity and positive predictive value of diagnostic methods.

Currently, there are two parts of the imaging evaluation of women with possible breast cancer. These are called screening and diagnosis. In the first, the patient has a mammogram with two views of each breast obtained and may also have clinical breast examination. If any suspect region is found on the screening mammogram, then the patient proceeds to the second part. In the second part, a radiologist uses those imaging methods that are available to determine whether or not this suspect lesion is real, and whether the positive predictive value is great enough that biopsy is indicated.

Currently, approximately 10% (range 4-14 %) of women having a screening mammogram are called back for diagnostic mammography. In the diagnostic workup, special mammographic views such as compression spot views, magnification views or special mammographic projection views may be obtained. The patient may also have sonography and or breast magnetic resonance imaging with gadolinium. In some centers imaging with 99m Tc Sestamibi may be used. This radiotracer labeled agent, approved by the FDA, localizes in breast cancer and some benign lesions.

After a full diagnostic workup, many patients are excluded from needing biopsy, but approximately 1/3 to 1/4 still need a biopsy. Of those who have a biopsy, 17-32% will have cancer based on the characteristics of the initial suspect region (some findings are more suspicious than others). With some patterns, the likelihood of cancer is close to 100%. But this still means that at least 2/3 of those having biopsy will not have cancer. This project, A Coordinated Approach to Breast Cancer Diagnosis (CABCAD) is designed to establish statistically supported criteria so that some of those women who now have biopsy and who are then found to have only benign disease, could be safely followed without biopsy.

II. KEY RESEARCH ACCOMPLISHMENTS: In the CABCAD protocol, women with a suspect lesion identified by screening mammography and/or clinical breast examination and who have had a current standard diagnostic workup with the recommendation of biopsy are recruited into the study. Each woman who agrees is then studied with both advanced imaging methods and with experimental methods. The standard methods are breast magnetic resonance imaging (MRI) with gadolinium enhancement and nuclear scanning with 99mTcSestamibi. At the time the study was initiated, Sestamibi was still an experimental agent for breast cancer evaluation. It is now FDA approved. Some of the women have had sonography as part of their standard breast imaging evaluation. The sonographic methods were upgraded to high resolution whole breast studies during the final year of the protocol. The experimental procedures incorporated into the original protocol were digital mammography, and sono-elastography, and (in pre-menopausal

women) nipple fluid was aspirated for cytogenetic analysis. In the original protocol, the Sestamibi imaging was imaged with both a standard gamma camera and with an experimental prototype high sensitivity high resolution dedicated breast gamma camera. During the study, we also started preliminary evaluation of electrical impedance imaging and spectroscopy.

We selected our clinical and experimental methods because each looks at a different biological spectrum of disease. The digital mammogram looks at anatomy; the sonography looks at tissue texture; the elastography evaluates hardness; the MRI evaluates microvasculature; the Sestamibi evaluates an unknown factor that is related to p-glycoprotein and mitochondrial localization probably based on molecular charge of the Sestamibi; the nipple aspirate fluid looks at cytogenetic lesions indicating biological change in the epithelium; electrical impedance looks at the spacing of cell membranes and vascularity of lesions. Of the available imaging studies likely to be useful in this differentiation, only positron emission tomography is not included because its great expense would likely preclude its eventual clinical application for this purpose.

Data from the CABCAD study are being used as research data for Ph.D. candidates in Electrical Engineering and Computer Science (at both Howard University and Catholic University of America). The educational activities with Howard University led to a Partnership Grant with Howard University to develop a formal curriculum in Electrical Engineering related to breast cancer detection and computer analysis of breast images. Currently two Ph.D. candidates are using the data (one at Catholic University of America and one at Howard University). A third (at Catholic University) has completed all work for his Ph.D. and will receive it this spring. We expect that this rich data source will be used for further analysis by several additional Ph.D. students.

A. Progress

- In the first year there was a long delay caused by disagreements between the consent forms as approved by the Georgetown University Institutional Review Board and the US Army Human Subjects requirements. Multiple versions were submitted until we arrived at one form acceptable to both. Project 2, was therefore officially started June 30, 1997. Since that time, we have initiated the protocol and have recruited 203 women into it. In the initial start up phase, scheduling problems were encountered so that not all patients could have all studies. The situation has recently improved, but scheduling problems became very severe in January, 1999 because of increased clinical demand on the MRI system. During much of the first part of this year delays in scheduling were 2-3 weeks, thus many women would have their biopsy prior to any chance of having the MRI. After intense negotiation that started in February, we were (starting in August, 2000) able to achieve a weekly 2 hour time slot for breast MRI research on the neural computational science research MRI system and the scheduling problem for MRI has resolved. Recently, there have been cutbacks in technologists available for sestamibi studies making scheduling more difficult, but this has not yet impacted the study. Due to all these problems, we have not been able to recruit as many patients as originally planned. Because of this we have continued the study until quite recently and have not yet therefore completed the statistical analysis; this analysis will be provided as a supplement to the Final Report.

- One of the sub-goals of this process was to use the cohort of patients under study to test new promising imaging methods, especially those developed by small companies that would not have the financial resources to fund their own full study. Thus, at the initiation of the project, we provided patients for study with an experimental breast sized gamma camera developed by PEM Technologies, Inc., Bethesda, MD. This experimental camera was used to test concepts for higher resolution nuclear imaging of the breast. Although the initial prototype was not successfully implemented because of the experimental nature of the process, 14 patient volunteers were studied. We have continued to work with this small business and have helped them with additional product design including a newly FDA approved system for nuclear medicine guided breast biopsy. In addition, we have worked with them on a breast biopsy localization system invented by PEM Technologies; this received an award of recognition at the 2000 Meeting of the Radiological Association of North America. The current device of the company (based on Positron Emission Mammography) was shown within one of the Keynote addresses at that meeting as a highly promising new technology. While these developments were not funded from the grant, this Cancer Center Grant has helped PEM Technologies to create these new devices that have received such positive recognition.
- A Second investigation of promise was the use of sono-elastography in the early part of this study. Sonoelastography is a promising new technology that allows one to use sequential ultrasound images to determine the hardness of breast lesions. During part of this Cancer Center project, sonoelastography was performed by one of our Investigators, Brian Garra, MD. Dr Garra has since left Georgetown but has continued work in this field with Jonathan Ophir, Ph.D. The concepts pioneered by these workers and a few others have now achieved major prominence with at least five papers on elastography at the recent SPIE Medical Imaging Conference in San Diego, February, 2001. The data acquired within this Cancer Center Grant has helped in the development of this new technology.
- We also used the cohort of patients in this project for early investigation of electrical impedance imaging and spectroscopy of the breast using a device invented by TransScan Ltd, Migdal Hameck, Israel. This device shows some promise in reclassifying borderline lesions as benign or malignant. The device has received FDA approval. We continue to work with the company because we believe that further improvements need to be made in the system. It clearly can provide detection information for many breast cancers and can exclude many benign lesions, but its current sensitivity and specificity are not sufficient for full clinical use. The company has recently brought us an updated software package that in preliminary trials done elsewhere has shown 95% sensitivity for cancer and an update of that will be installed next week. We consider the results with the modified system highly promising and will continue to work with this FDA approved, but from our standpoint, still experimental device for breast lesion classification.
- We have also worked with a new company, Imperium Limited, which has an experimental transmission ultrasound system suitable for breast imaging. This device is still a laboratory prototype, not yet suited for clinical research, but we are working with the company to incorporate it into clinical trials in the future.

- **Table 1** indicates the number of patients recruited into each arm of the study and the biopsy results to date. *The updated chart will be submitted as a supplement when statistics are complete.*

Table 1: Biopsy Results of Patients Evaluated

Biopsy Results	No. Patients	Percent
Cancer	20	11
DCIS	8	4
LCIS	3	1
Atypical hyperplasia	7	4
Fibroadenoma	18	10
Other benign	59	32
Results pending	46	25
No biopsy performed in spite of original recommendation for biopsy and biopsy pending	23	13
Total Evaluated	184	100

- The goal of this study is to try to find women with suspect lesions requiring biopsy that do not have cancer. Cancer was found in 11% and DCIS in 4% of women going to biopsy. Because the goal is to find features on imaging studies that indicate that the disease is a benign process, we need many benign cases for our analysis and consider this an appropriate ratio of benign to malignant lesions. The patients that have been recruited thus far are representative of the population of women who go for breast biopsy at Georgetown University Medical Center. For the 184 patients evaluated to date, **Table 2** demonstrates our success in completing the diagnostic studies and the reasons that studies were not conducted.

Table 2: Results of Procedures being Utilized *This chart will be updated in the statistical supplement that will be provided later.*

Procedure	Participants	Comments
Nipple aspirate fluid (NAF)	26 of 184 (14%)	NAF attempted on 75 patients. Of these, 40 were post-menopausal (only 1 yielded fluid). Of the 35 premenopausal women, 13 had never been pregnant, 3 had had extensive prior breast surgery, 4 yielded no fluid, and 4 yielded insufficient fluid for processing
MRI	104 of 184 (56%)	22 excluded by criteria 5 refused 10 too large 24 not done due to scheduling problems on scanner
Nuclear Sestamibi imaging on Standard Gamma Camera	151 of 184 (81%)	7 refused 8 no available time on machine
Ultrasound	58 of 184 (31%)	Not part of original protocol

Due to continuing scheduling problems, many patients were unable to be scheduled for all studies. The situation improved in 2000 as new approaches were developed for assuring schedule availability..

- Nipple Aspiration experience:** The low overall yield in the nipple aspirate studies reflects the large proportion of post-menopausal women, scheduling problems precluding an attempt at nipple aspiration (57 of 184 patients, 31%) and high refusal rates (52 of 184 patients, 28%). One of the reasons for the latter may have been that many of the women were referred by physicians who emphasized the imaging tests that they would receive but did not explain the nipple aspiration procedure. This will be clarified with further analysis of the data collected by the Outcomes Core as part of the Patient Satisfaction Survey (*to be included with statistical supplement that will be provided later*). However, it is important to note that, of the 35 premenopausal women for whom nipple aspiration was attempted, the yield of usable fluid (i.e. more than 1 drop) was 25 of 35 or 71%, which is very consistent with the experience of most investigators who use this technique. The difficulties with scheduling have meant that the clinical coordinator was often rushed in the procedure, which is particularly a problem with the postmenopausal women. Because they are known to be less likely to yield fluid, it is essential that sufficient time be allowed for adequate “milking” of the breasts, to move fluid forward through the ducts toward the nipple. Most investigators recommend at least 5 minutes just for this part of the procedure (for each breast). However, the clinical coordinator was sometimes left with only 10 minutes to do the entire aspiration procedure, which we feel may have strongly influenced our low yield with postmenopausal women (typical yields by other investigators with this group are in the range from 10-30%). Furthermore, other investigators using the nipple aspiration procedure have also emphasized that it is

important for the patient to feel relaxed, which is also compromised when scheduling problems result in the procedure being rushed. We did conduct (in October, 2000) an in-service with a clinical coordinator from Dr. Susan Love's Breast Clinic. She did not identify any differences in the techniques that we were using, compared to their techniques, although she again stressed the importance of a relaxed environment with adequate time. Surprisingly, of the patients that she worked with that day (not only CABCAD patients, but others being seen at Lombardi Cancer Center) she thought that the patients in general seemed more tense than those she was used to working with. This may reflect the fact that her patients have generally discussed the procedure with Dr. Love and may have even sought her out to receive the procedure. Other factors contributing to increased tension in our patients may be the time commitment required to undergo multiple imaging tests.

In our original proposal we had planned to test the nipple aspiration fluid (NAF) samples for p53 by immunohistochemistry and erbB-2 by ELISA. However, our initial attempts with procedures were negative, probably because of the low sample volume and low cellularity. We were also concerned that the number of patients with p53 mutations or erbB-2 overexpression in their tumors is only in the range of 20-35%. We decided to try a different biomarker, namely comparative genomic hybridization (CGH), a test for non-specific chromosomal gains and deletions that spans the entire genome. This approach was chosen because we feel that it is likely that rather than a specific genetic lesion being present in a majority of tumors, it is most likely that tumors are characterized by a number of different genetic defects, which could be detected by a non-specific approach like CGH. However, to do this required a larger quantity of DNA than could be obtained from the relatively low cellular content of NAF samples (10 epithelial cells is a typical cell count). We developed a technique to grow the NAF-derived cells in culture (we believe we are the first to have achieved this) to expand the cell count enough to yield sufficient DNA to perform CGH (Haddad 1998). Although we have been able to get this technique to work, in our hands the success rate for expansion of the cell population (approximately 25%) is too low for this to be a useful diagnostic approach. We are now investigating whether breast ductal lavage (BDL), a technique that has been improved recently by Susan Love and colleagues, may circumvent this problem for future studies that we have planned. The BDL technique yields cell counts on the order of 10^3 to 10^5 , an amount that is more than adequate for conducting CGH without the need for the intermediate culturing step. Another approach that we are exploring in an NCI-funded study is to evaluate proteomic expression patterns in NAF. This technique, based on surface-enhanced laser desorption and ionization spectroscopy (SELDI) can detect secreted proteins in as little as 1 microliter diluted 1:100. This approach may identify early functional abnormalities that reflect early malignant phenotype.

In sum, we feel that the NAF approach still has promise, but further biomarker development is necessary to identify markers that are amenable to the small volumes obtained with NAF, or to try alternatives such as BDL that provide more cellular samples. Finally, the NAF approach is of uncertain utility in postmenopausal women.

- **Findings on imaging studies:** *This data will be updated when statistical analysis is complete and will be provided in a supplement.*

1 Invasive Breast Cancer: 20 cases.	MRI: Positive in 8, negative in 2. Not done in 10. Sestamibi: Positive in 10, negative in 6, Not done in 4.
2. DCIS : 8 cases.	MRI: Positive in 3, negative in 3, Not done in 2. Sestamibi: Positive in 5, negative in 2, patient motion in 1.
3. Atypical Ductal Hyperplasia: 7 cases	MRI: Positive in 1, negative in 6 Sestamibi: Positive in 1, negative in 4. Not done in 2.
3. Fibroadenoma: 18 cases	MRI: Positive in 1, benign in 12, not done in 5. Sestamibi: Positive in 5, negative in 9, not done in 4.
4. Other benign: 59 cases	MRI: Positive in 5, Indeterminate in 2, Benign in 20, 32 not done Sestamibi: Positive in 9, equivocal in 4, Benign in 17, 29 not done

Other small group categories: LCIS 3 cases. Papillomas 7.

B. New research information that is relevant to this study

- Comparative evaluation of conventional vs. digital mammography: We have completed additional prospective evaluation of the digital mammography system that we are using in this protocol. We evaluated this system in a series of 134 cases that included 23 cancer cases. Six radiologists with no prior experience with digital mammography were, on average, better at distinguishing benign and malignant lesions on the digital images than on conventional high quality original mammograms. This result did not achieve statistical significance with this sample size, but the trend is clearly shown in Table 4. The data has been presented in the SPIE Medical Imaging Conference in February, 1997 and published in their proceedings. The digital mammography system we used was developed by Fuji Photo Film Corporation. On the completion of this project that showed equivalence of digital and conventional mammography, we considered that all available gain from this system had been achieved and that the system was equivalent, but not superior, and did not need further investigation. We had seen a prototype of a higher resolution (50 micrometer pixel size) system in Japan in 1994 in the Fuji Research and Development Center in Myanodai, Japan, and in November, 2000, the system was shown for the first time at the 2000 Meeting of the Radiological Society of North America. Fuji has offered Georgetown the use of the new system for clinical research and we are in negotiations with them for access to this system for research. The image

quality is extremely impressive and should, we believe, increase the detection rate of small breast cancers. The results from our experimental work within this cancer center grant help to encourage Fuji to continue with commercialization of the new system.

Table 4 demonstrates the average true positive fraction at each false positive fraction for the six readers in a study comparing 24 cancers and 25 lesions that at biopsy were shown to be benign. Digital and conventional images were compared.

Table 4

Reader	#1	#2	#3	#4	#5	#6	Average
Digital	0.600	0.656	0.735	0.697	0.462	0.643	0.633
Screen-film	0.609	0.616	0.556	0.575	0.495	0.644	0.583
p-value	0.923	0.637	0.085	0.069	0.741	0.992	

Table 4 shows the individual ROC areas under the ROC curves for each of the six readers as well as the average of these six values. The digital system is on average, better, but these results do not reach statistical significance with this relatively small sample size.

There have been additional publications on digital mammography performed elsewhere. These articles have all be based on variations of the Storage Phosphor technique that we have been using or an alternate method we demonstrated and reported on in 1993. Findings by Hundertmark, Cowen, Funke, and Perlet agree with our basic findings that this method of digital mammography is equivalent to conventional mammography. An article by Kheddache indicates that the system is not as good as screen film conventional mammography. A digital mammography system developed by General Electric has been studied at the Universities of Colorado and Massachusetts. Partial data from this has been submitted for publication and has been presented at meetings. The data suggest that its performance is equivalent to conventional mammography, but with, perhaps, fewer false positive detections. Non-published information from other systems suggests that so far none of the competing systems under test have shown clinical advantages compared to screen film conventional mammography, but may be equivalent. Until recently, we were performing pilot work under contract with Siemens Corporate Research to determine whether their proprietary image processing of 50 micron pixel digitized mammograms can disclose breast cancer in women in whom the cancers were not mammographically visible. This contract ended when Siemens Corporate Research decided to suspend the development of this image processing algorithm.

- FDA approval for Sestamibi: At the time of the original grant submission, 99mTc Sestamibi had not completed evaluation by the FDA for use as a breast cancer imaging agent. This evaluation has now been completed and Sestamibi has received FDA approval for this purpose.

There have been additional studies published comparing the accuracy of breast MRI and Sestamibi. In order for any test or group of tests to meet the requirements for avoiding breast biopsy, very high negative predictive values are necessary. Results reported by Palmedo show a negative predicted value (NPV) for Sestamibi of 83% and for MRI of 75%. Fenlon reports NPV for Sestamibi of 95% and for MRI of 91%. Helbich reports NPV of 81% for Sestamibi and 98% for MRI. Helbich's results are unusually good for NPV of MRI and less than usually reported for Sestamibi, for uncertain reasons. It is likely that the variability of results reflect different characteristics of the patients included in each study. Because of this, we are recording in our database detailed information about the clinical and mammographic findings in each case. As we continue to analyze our data according to several key mammographic features, we expect to better define breast lesion characteristics that would indicate those patients in whom MRI and/or Sestamibi would be expected to have sufficiently high NPV to permit follow-up rather than requiring biopsy.

It is clear from the data acquired so far that the choice of an appropriate method for preventing breast biopsies for benign disease will require a careful assessment of the information available from the mammogram and ultrasound. A flow chart of our results is likely to be based on several of the BIRADS criteria and ultrasound descriptors as we do not anticipate a simple answer to the problem. If this effort developing this flow chart is successful, we would then be able to provide a flow chart such that one could say that if one has a mammographic lesion with the following group of characteristics, then MRI and/or Sestamibi would likely provide the best information to help avoid a biopsy; or alternatively, that for a lesion with those characteristics, neither method would be expected to provide sufficient added information so that biopsy could be avoided.

C. Changes in protocol: During the duration of this project we have maintained a centered focus on the comparison of 99mTcSestamibi and MRI. Other specific sub-projects have been started and stopped as the value or lack of value of new tests was established.

- We eliminated the experimental test of sono-elastography. In the first year of the protocol, the investigator of this technique was unable to provide us with an interpretation of his data. He has left the institution so that the machine for elastography is no longer available. This data has, however, continued to be used by him and by Jonathan Ophir, Ph.D. in their research.
- We suspended the use of the breast sized dedicated gamma camera because of technical problems in its operation. The inventor of this system had indicated that a new system was being built and would become available. He has now indicated that the newer system will not perform to meet our requirements and that he has stopped development. As indicated above, however, this data has led his company, PEM Technologies, Bethesda Maryland, to continue development work. They have a new FDA approved system for nuclear medicine guided biopsy and, under development, a positron emission mammography system.

- We joined in a grant proposal with another investigator (Harry Barrett, PhD, University of Arizona) regarding a differently designed high resolution gamma camera. This new small field of view camera has a resolution of 0.2mm, a high enough resolution that the only feature degrading the image would be patient motion and scatter within the breast. Because of its small field of view, accurate positioning would be achieved by ultrasound performed in the Nuclear Medicine facility immediately prior and in the same position used for the Sestamibi imaging. This proposal was funded, but additional tests of the very high resolution gamma camera showed that it did not meet design specifications. Work is continuing, but we have not tested the revised system.
- We have added high resolution ultrasound to the protocol. The investigative work by ATL Corporation has shown that high resolution ultrasound can in some instances provide improved assignment of breast masses into benign and malignant categories. This technology is only recently available to us and we have incorporated it into the protocol. We have also added Doppler measurements of blood flow in breast lesions. Data available from the literature leaves uncertainty as to its benefit in differentiating breast cancer from benign masses. In addition to this project, we have started to acquire pilot data to test a new hypothesis: In a woman with an identified breast cancer, the concern is that there may be a second primary cancer or that the extent of the cancer may be larger than that identified by mammography. MRI has been recommended as a method for better defining the extent of tumor and the presence of second primary lesions. As a pilot project we will be comparing whole breast ultrasound to MRI for the measurement of the extent of tumor and for the presence of second primaries. To date, we have not found any second primary cancers on ultrasound.
- Other technologies under investigation: We have been working with TransScan Medical (Ramsey, NJ), a company that has developed a method to record electrical activity from the breast and from breast cancer. Data acquired by TransScan led to FDA approval of this device for improving the decision between BIRADS 3 and low grade BIRADS 4 lesions. During the summer of 1999, we had the machine at Georgetown and did extensive tests of it related to electronic reliability and to develop a phantom to better understand how it works. We found that the machine could indeed detect both benign and malignant lesions in the breast, but that the electrical reliability of the machine's measurements were different from actual electrical values input into the machine and varied under different test situations. The company has offered us 24 months use of the updated model of the machine for incorporation into this project. The data submitted to the FDA indicated that the combination of TransScan with Mammography increases the specificity of mammography and that this effect is greatest in women under the age of 50. It is therefore a good fit for inclusion in this project.

Table 5. Data submitted by TransScan to the FDA in the Approval Process. TransScan received FDA approval June, 1999.

	Sensitivity	Specificity
TransScan Alone	69%	45%
Mammography alone	82%	39%
TransScan and Mammography	86%	51%

	Sensitivity	Specificity
Under 50 yrs	81%	76%
Over 50 yrs	76%	66%

In our own tests, we found that the system behaves somewhat inconsistently and needs further improvement. The software and hardware for this system have been updated and a new software package will be replaced next week. We continue to work with the company to improve this system. The work of others suggests that the sensitivity for cancer detection with the new software of 95% in a small series of patients.

- We are providing data from the breast MRIs obtained as part of this study to our research partners at Catholic University: Joseph Wang, PhD and his PhD student Kelvin Wood for their work on a US Army funded project to improve the visualization of breast cancer on breast MRI examinations through 3D visualization methods and change detection. Dr. Wood has fulfilled all requirements for the Ph.D. and will receive his degree in June, 2001. The project is continuing with two graduate students, one from Catholic University. A second project using the data is underway with a Ph.D. student from Howard University who will be working on image fusion of the multimodality images obtained in this project.

D. Clinical and Economic Outcomes: We are collecting information on patient satisfaction, test acceptability, and costs using materials developed by Core 2.

E. Data acquisition and analysis: Because of the shortened time-frame available for this project, we have not yet completed data analysis. This data will be provided as a supplement to this report.

III. CONCLUSIONS: Project 2, A Coordinated Approach to Breast Cancer Diagnosis was successful in recruiting patients and gathering data on patients with both benign and malignant disease. We have encountered significant scheduling problems based on cutbacks in Medical Center technical personnel and equipment availability. In the final year of the project we were able to solve the scheduling problems that had plagued us as the Medical Center learned to cope with severe austerity. The results of the correlation of Sestamibi with mammographic categories are being analyzed and are being prepared for presentation. We have added high resolution ultrasound and Doppler measurements to our protocol and have explored as a pilot project its

substitution for MRI for the detection of second breast primary tumors and measurements of disease extent. We have changed several aspects of the protocol based on new knowledge.

The project provided opportunities for the correlated analysis of several potentially highly promising new methods for breast imaging including digital mammography, sono-elastography, high resolution gamma camera and electrical impedance imaging of the breast. Each of these new technologies has shown improvement over the time of the project. The data from this project was used by one graduate student in Computer Science as part of his research database for his Ph.D. degree. Two additional Ph.D. students in Computer Science and Electrical Engineering are now using the data from this project for their own Ph.D. research. Based on the affiliation with Howard University, we have instituted a new Partnership Grant to help train their Electrical Engineering graduate students in aspects of breast disease and imaging. While we have not succeeded in the primary goal of finding methods to avoid breast biopsies that show only benign disease, the project has resulted in several advances in new imaging methods for breast cancer and in the training of Computer Science and Biomedical Engineering students who can continue to advance the field. We have been able to assist several small companies in their development of new promising technologies utilizing nuclear breast imaging, nuclear imaging guided breast biopsies, electrical impedance imaging and spectroscopy, and in the development towards a new transmission ultrasound system for breast imaging and image guided biopsy. This project has resulted in additional successful grants in experimental ultrasound development and testing, electrical impedance imaging and spectroscopy, and in a Partnership grant for training Computer Science and Electrical Engineering Students in aspects of imaging breast disease.

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PROJECT 3: DEVELOPMENT OF NOVEL ANTIANGIOGENIC THERAPIES IN METASTATIC BREAST CANCER

I. INTRODUCTION: The overall purpose of this proposal was to evaluate the clinical benefits of inhibitors of angiogenesis in regards to improving the care of patients with breast cancer. To accomplish this goal, we performed Phase I and II studies of agents that have been shown in preclinical studies to inhibit breast cancer associated angiogenesis: thalidomide and TNP470. We complemented these clinical trials with studies of the quality of life of participating patients, as well as with studies of the cost effectiveness of application of these agents in comparison to standard care.

Both the fumagillin derivative, TNP-470; and the sedative, thalidomide, had been shown to have anti-neovascular and anti-neoplastic properties in preclinical studies, and phase I studies of these drugs were either completed or underway at the time of our original proposal.

Clinical trials directed toward accomplishment of our goals and aims were completed during the funding period of this grant. We have published the results of our Phase II study of thalidomide in a major oncology journal (the Journal of Clinical Oncology). We have reported the preliminary results of our Phase I study of TNP470 plus paclitaxel at a national meeting, and a manuscript describing the final results is being prepared. We are now considering whether our preliminary results justify a phase III trial in which paclitaxel plus TNP470 will be compared to paclitaxel alone. The following sections will summarize our final results.

II. BODY

A. HYPOTHESIS/PURPOSE: We hypothesized that incorporation of well-tolerated antiangiogenic agents into standard treatment regimens for breast cancer will increase progression free survival, improve quality of life and, due to fewer treatment related side effects, decrease health care costs. Because these agents are unlikely to result in objective, measurable tumor regressions, we felt it was necessary to develop innovative trial designs to document their efficacy.

B. TECHNICAL OBJECTIVES: These objectives were to be met by a collaboration between the clinical investigators in Project 3 and the investigators from the Quality of Life and Clinical Economics Core (Core 2). This section of the Final Report will only cover Technical Objective 1. The other two will be covered in the Report describing the results from the Core.

1. To evaluate the antitumor activity of novel, non-cytotoxic antiangiogenic agents for the treatment of metastatic breast cancer in Phase I and Phase II trials. Of note, we originally proposed to initiate a phase III study of one or both of these agents. However, as described below, our results in the Phase I and II studies were insufficiently promising to justify accrual of patients to a Phase II trial.

2. To evaluate the impact on quality of life of non-cytotoxic antiangiogenic agents in a diverse spectrum of patients with metastatic breast cancer.
3. To evaluate the cost-effectiveness of non-cytotoxic antiangiogenic agents in patients with metastatic breast cancer.

C. OVERVIEW OF CLINICAL TRIALS OF ANTI-ANGIOGENESIS: In our initial proposal, we planned two separate clinical trials of anti-angiogenic agents. In the first, we proposed to test the activity of the angiogenic inhibitor, TNP-470, using a novel trial design. In a second study, we proposed to test the efficacy of oral thalidomide, in a randomized phase II clinical trial. After some initial adjustments in trial design, we completed accrual to a Phase I study of the combination of weekly paclitaxel plus TNP470, and we completed a Phase II trial of thalidomide trial. The pre-clinical data and rationale for these studies was fully presented in our original proposal and annual updates.

1.0 Studies of TNP470 and paclitaxel.

In a previous report, we provided evidence that the combination of TNP470 and paclitaxel is of interest. Prior Phase I studies with TNP470 alone demonstrated that the plasma half life of TNP470 is very short. Preclinical evidence suggests that paclitaxel may prolong the half-life of TNP470, presumably by reducing hepatic clearance. Moreover, paclitaxel alone has demonstrated anti-angiogenic activity. Finally, recent studies from other sites have demonstrated that paclitaxel can be administered weekly with an excellent safety profile.

Revised Research Plans. Taken together, these results suggested that the combination of paclitaxel and TNP-470 might result in both direct tumor cell cytotoxicity due to the paclitaxel and, more germane to this proposal, to additive and perhaps synergistic suppression of angiogenesis due to both drugs. However, the precise dose, schedule and toxicities of combining these two agents have not been determined.

We therefore proposed to delay initiation of a randomized trial while we performed a pilot phase I clinical study to determine whether weekly administration of paclitaxel, coupled with simultaneous TNP-470, is safe, and to determine the MTD of TNP-470 when delivered in combination with paclitaxel. The endpoints we will use to make this decision include pharmacokinetics (TNP-470 levels), toxicities, convenience of drug delivery, and overall cost of administration.

The pilot trial of weekly paclitaxel and TNP-470 in patients with any metastatic malignancy that is refractory to standard therapy or for whom paclitaxel would be considered appropriate therapy is now completed. We preferentially placed any patient with breast cancer for whom paclitaxel was a reasonable treatment option on this Phase I trial. We chose this strategy for the following reasons: 1) there is no reason to believe that the toxicities and pharmacokinetics observed in patients with other solid tumors would not be applicable to patients with breast cancer; 2) paclitaxel is active in many malignancies, and the schedule to be tested is novel and may have even greater activity than that used in the standard clinical setting; and 3) wider eligibility hastened our ability to complete this pilot and move on with the breast cancer-specific randomized trial.

We initially considered a randomized trial comparing paclitaxel vs. paclitaxel plus TNP-470 in patients with metastatic breast cancer, using the paclitaxel and TNP-470 dose and schedule selected from the pilot. However, in the interest of patient concern, we have not proceeded with this trial due to the relative lack of apparent enhanced efficacy of the combination of paclitaxel and TNP470 as it was delivered in this Phase I trial.

III. KEY RESEARCH ACCOMPLISHMENTS

1.0 Clinical Trial Results: Pilot Trial of Paclitaxel and TNP-470 II. Weekly 1 hr Infusion Paclitaxel plus TNP-470

In anticipation of initiating a prospective randomized trial of paclitaxel with or without TNP-470, we performed a Phase I study of the optimal dose of this combination of drugs, using a relatively novel schedule. We simultaneously studied circulating anti-angiogenic activity in serum of patients receiving this combination.

Eligible patients who signed the consent form were administered TNP 470 as a 4-hour infusion on day 1. Paclitaxel was administered starting on day 8 as a 1-hour infusion, followed by TNP-470 as a 4-hour infusion. The second and subsequent cycles were administered at 1 week intervals from the first day of Paclitaxel infusion. For each cycle, Paclitaxel was administered as a 1 hour infusion with TNP-470 given as a 4-hour infusion on the same day as Paclitaxel treatment. All treatment was done on an outpatient basis.

Table 1. Treatment Plan for paclitaxel plus TNP-470.

	First Cycle					Subsequent Cycles			
	D1	D8	D15	D22	D29	D1	D8	D15	D22
TNP-470	X	X	X	X		X	X	X	
Paclitaxel		X	X	X		X	X	X	

Progress to Date: As of February 2001, twenty-two patients were entered into this Phase I trial. This trial is now closed to new accrual, and all but one patient have progressed and are off study. Patient characteristics are provided in Table 2.

Table 2. Characteristics of patients entered onto Phase I trial of paclitaxel + TNP-470.

Dose Level	Disease	Gender	Age	Race
I	Cervical Cancer	F	49	Caucasian
	Anal Cancer	M	52	Caucasian
	Cancer of Unknown Origin	M	50	Caucasian
II	Ovarian Cancer	F	43	Hispanic
	Breast Cancer	F	44	Caucasian
	Breast Cancer	F	75	Caucasian
III	Breast Cancer	F	64	Caucasian

	Lung Cancer	F	52	Caucasian
	Mesothelioma	M	66	Caucasian
IV	Breast Cancer	F	66	Caucasian
	Carcinoid Tumor	M	36	Asian
	Prostate Cancer	M	52	Caucasian
	Ovarian Cancer	F	56	Caucasian
	Cervical Cancer	F	43	Caucasian
	Breast Cancer	F	45	Caucasian
	Cancer of Unknown origin	M	51	Caucasian
V	Soft Tissue Sarcoma	M	71	Caucasian
	Lung Cancer	F	54	Caucasian
	Cholangiocarcinoma	F	74	Caucasian
VI	Lung Cancer	F	34	Caucasian
	Ovarian Cancer	F	54	Caucasian
	Lung Cancer	M	52	African American

Toxicities: Toxicity data for all dose levels are summarized in Table 3. Predominant toxicities consisted of nausea/vomiting, diarrhea, hair loss, fatigue and myelosuppression believed to be due to Paclitaxel. One patient on dose level 3 and two patients on dose level 4 developed peripheral neuropathy attributable to Paclitaxel. One of these patients (on dose level 4) required reduction in the dose of Paclitaxel. Dose level 4 was therefore expanded to include a total of six evaluable patients. One patient each on dose levels 3, 4 and 6 developed transient ocular scotomas shortly following drug infusion. One of these patients (on dose level 3) was removed from study due to recurrence of scotomas on re-treatment. Since ocular scotomas have been previously reported with Paclitaxel, this toxicity was felt to be attributable to Paclitaxel. Five patients developed lightheadedness/dizziness, and one patient on dose level 4 developed decreased memory and difficulty finding words. These toxicities have been previously observed with TNP-470 alone.

Table 3. Toxicities for patients enrolled in Phase I trial of paclitaxel and TNP-470 (all toxicities are Grade 1-2)

Toxicity	Dose Level					
	1 TNP-470 (88.5) Taxol (70)	2 TNP-470 (88.5) Taxol (80)	3 TNP-470 (133) Taxol (80)	4 TNP-470 (133) Taxol (90)	5 TNP-470 (177) Taxol (90)	6 TNP-470 (177) Taxol (100)
Nausea/Vomiting	1	0	0	4	0	1
Diarrhea	0	0	1	2	2	1
Fatigue	1	2	2	3		
Anorexia	0	0	0	3	1	0
Mucositis	1	0	0	0	0	0
Leukopenia	1	0	0	2	0	0
Anemia	1	1	1	0	0	1
Thrombocytopenia	1	0	0	0	0	0
Lightheadedness/ Dizziness	1	0	1	0	1	2
Insomnia	0	0	0	0	1	0

Mood changes	0	1	2	0	0	1
Hair Loss	0	0	0	1	0	0
Peripheral Neuropathy	0	0	1	3	2	1
Ocular Scotomas	0	0	1	1	0	1
Decreased Memory	0	0	0	1	0	0
Taste alteration	0	0	0	1	0	1

Pharmacokinetics: Serial plasma samples have been collected from these patients. Plasma pharmacokinetics of TNP-470 are being performed by TAP pharmaceuticals. Plasma pharmacokinetics of paclitaxel were found to be consistent with those reported in the literature as shown in the table below.

Table 4. Pharmacokinetic parameters of paclitaxel administered as a one-hour infusion (mean \pm SD).

Dose (mg/m ²)	Number of patients	AUC (μ g/ml*hr)	T1/2 (hr)	Cmax (μ g/ml)
70	3	2.5 \pm 0.40	9.17 \pm 0.40	1.55 \pm 0.49
80	5	4.58 \pm 0.81	7.57 \pm 3.34	3.11 \pm 1.25
90	4	3.51 \pm 1.11	6.19 \pm 2.42	2.51 \pm 0.58
100	3	2.94 \pm 0.53	6.43 \pm 0.49	2.20 \pm 0.59

Efficacy/Response: Partial response (>50% tumor reduction) was observed in two patients (ovarian cancer lasting ~1 year and mesothelioma lasting ~ 4 months). Of note, the patient with ovarian cancer had previously progressed after treatment with paclitaxel alone. A minor response (~25% tumor reduction) was observed in a patient with metastatic breast cancer lasting 1.5 years, while one patient with hemangiosarcoma had stable disease for nine months during treatment.

Biologic Assay for Anti-angiogenic Activity in Plasma: An endothelial cell proliferation assay is being utilized to study the biologic activity of this drug combination. Preliminary data indicate that paclitaxel and TNP-470 may have additive anti-angiogenic activity. Sample analysis is ongoing at this time.

The results of these studies were reported at the 2000 meeting of the American Society of Clinical Oncology, and a manuscript describing these studies is attached in the appendix packet.

Summary of TNP-470 Pilot Studies. In summary, preclinical data suggest that the combination of paclitaxel and TNP-470 might be additive if not synergistic as a result of additive anti-angiogenic effects. We performed this pilot, Phase I study to determine if the combination of the two drugs, delivered weekly, was tolerable, and to determine the MTD. In that regard, toxicity data showed that the combination of TNP-470 and paclitaxel was well tolerated up to the MTD of both drugs (177 mg/m² of TNP-470 and 100 mg/m² of paclitaxel).

We initially proposed a prospective randomized trial. Although the phase I trial was not performed to determine efficacy, our overall impression was that the combination did not result in substantially higher response rates than we might have expected in this population. However, because this was a phase I study with a very heterogeneous group of patients, many of whom were heavily pre-treated, we cannot say that the combination is not sufficiently exciting to proceed. As noted, the pharmacokinetic and biologic correlative data provide some suggestion that the combination may have some degree of synergy.

These data will be published, and we plan to continue dialogue with our colleagues in the oncologic community regarding whether and what type of followup clinical trials should be performed. Of note, an ongoing phase I trial at our institution is evaluating TNP-470 given by a continuous 120-hour infusion. Future plans might include exploring the possibility of combining weekly paclitaxel with a 120-hour infusion of TNP-470.

2.0 A Phase II Clinical Trial of Thalidomide with Pharmacologic and Growth Factor Monitoring.

Overview. As described in our initial proposal, the sedative thalidomide has been shown to have potent anti-angiogenic activity in preclinical models. Indeed, it has recently been approved for clinical use in this country for non-neoplastic diseases, with the caveats necessary to avoid exposure to pregnant women.

We therefore chose to pursue a randomized Phase II study of thalidomide in patients with breast cancer. We have now fully completed accrual and followup of patients on this trial. The results were presented in abstract form at the American Society of Clinical Oncology Annual Meeting in May, 1999 (Atlanta GA) and have now been published in the Journal of Clinical Oncology (see Baidas, et al in Appendix). The following is the final report of the clinical and correlative science aspects of this study. The QOL, and cost studies will be reported separately.

Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer

Patients accrued to Thalidomide: Twenty eight patients were been accrued at the four centers (Table 5). Fourteen patients were accrued on each of the two dose levels. All patients were women with metastatic breast cancer. Patient characteristics are presented in Table 6.

Table 5: Accrual to Phase II Thalidomide Trial by Site

Dose	Georgetown	Dana Farber	Chicago	Duke	Total
200mg	6	4	3	1	14
800mg	9	3	2	0	14
Total	15	7	5	1	28

Table 6: Patient Characteristics

Characteristic	200mg	800mg
Age		
30-40	1	3
41-50	7	2
51-60	5	4
61-70	0	4
71-85	1	1
Prior Chemotherapy regimens		
0-1	2	2
2-3	12	12
ABMT	3	2
Number of Hormonal Therapy		
0-1	7	5
2-4	7	9
Site of Disease		
Bone Only	1	0
LN only	3	1
Liver Only	1	1
Chest Wall	1	0
2-4	8	12

Patient Outcome and Dose modifications:

All patients have been removed from the study due to progressive disease except two patients. The first was removed due to grade 3 peripheral neuropathy and the second refused to continue treatment on study due to mild side effects (refused dose reduction). One patient at the 200mg dose required dose reduction due to grade 3 neuropathy. At the 800mg dose, four patients had to reduce dose to 600mg and two patients to 400mg, all due to neurotoxicity (somnolence). Three patients continued at the 800mg dose with no changes.

Duration of treatment:

At the 200mg level, one patient was taken off study at 2 weeks and a second patient at 4 weeks from starting treatment due to progressive disease. Ten patients were taken off at 8 weeks due to progressive disease at the time of staging. Two patients went beyond the first 8 weeks staging, one was removed from study at 11 weeks due to G3 neuropathy, and the second at 16 weeks due to progressive disease at the time of staging.

At the 800mg level, two patients were removed from study at 4 weeks, one due to progressive disease and the second refused to continue treatment due to side effects (also, refused dose reduction). Four patients were taken off study at six weeks due to progressive disease and eight patients were taken off at 8 weeks due to progressive disease. None of the patients at the 800mg continued beyond the first eight weeks of treatment.

Adverse Events:

Only one patient was removed from the study due to grade 3 neurotoxicity (peripheral neuropathy). This patient was on the 200mg dose and was removed at week 11. The main dose limiting toxicity was somnolence (grade 2) requiring dose reduction at the 800mg dose level.

The dose was reduced from 800 mg to 600mg for four patients, and from 800 mg to 400mg dose for two patients. The other adverse events did not require dose reduction or removal from the study.

Table 7: Adverse Events for Patients on Thalidomide

Adverse Event	Number of Patients Treated at:		Total
	200mg	800mg	
Constipation	3	10	13
Somnolence	4	8	12
Fatigue	6	6	12
Peripheral neuropathy	5	4	9
Dizziness and Instability	2	4	6
Dry Mouth	2	6	8
Skin rash	1	2	3
Nausea	0	2	2
Anorexia	1	1	2
Arrhythmia	1	0	1
Neutropenia	1	1	2
Headaches	1	0	1

Efficacy/Response to Treatment:

Response: No patient achieved partial or complete response.

Time to Treatment Failure/Progression. In addition to determining response, we also prospectively assessed evidence of failure to progress at eight weeks, with the assumption that to do so in a group of patients with previously progressive disease would indicate activity of the drug. Two patients at the 200mg dose had stable disease at the 8 weeks staging. The first patient had reduction in the hilar and mediastinal lymphadenopathy (only site of disease) by 47% at the 8 weeks staging. However, at the 16 weeks staging, she had progressive disease at that site and was removed from the study. The second patient had chest wall disease that was slowly progressing on no treatment over the last twenty months before starting thalidomide. At the 8 weeks staging she had stable disease, she was removed from the study at week 11 due to grade 3 peripheral neuropathy.

Thirteen patients at the 800mg dose had progressive disease at 8 weeks or before, and none went beyond the first 8 weeks. One patient refused to continue treatment beyond week 4 due to side effects and refused dose reduction.

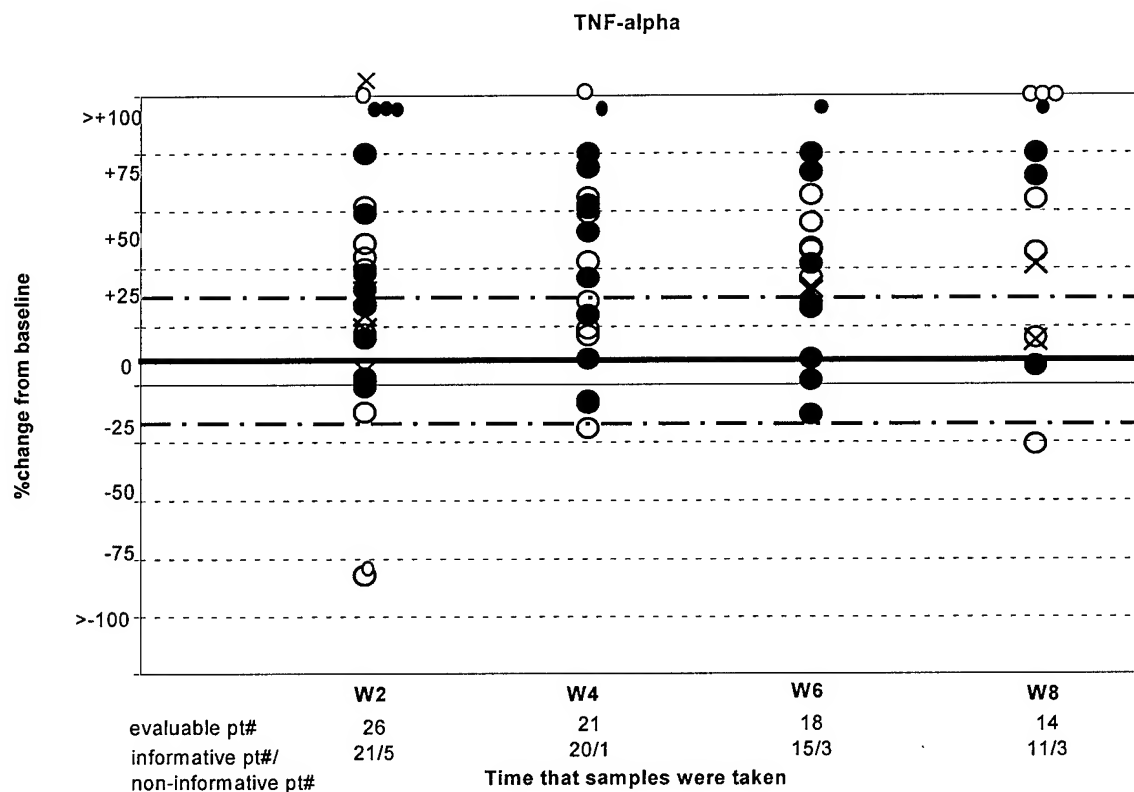


Figure 1. TNF-alpha Levels During Thalidomide Treatment. Open Circles=800 mg/day. Closed Circles= 200 mg/day. X=Uninformative Patients (TNF=alpha levels never above normal cutoff).

Correlative Science:

Circulating Angiogenic Factor Levels. At base line, 5 of 27 (18.5%), 6 of 27 (22.2%), and 13 of 27 (48.1%) patients had elevated levels (\geq mean + 1SD in normal population) of bFGF, VEGF, and TNF- α respectively. Serial bi-weekly changes in serum bFGF, VEGF, TNF- α and MMP-9 are illustrated in Figure 1. Patients were only included in this analysis if their marker levels were elevated at some point (baseline or follow up). Non-informative patients (patients whose marker levels were never above a cut off of the mean +1 SD of a normal population) were not included. A change of 25% or more from baseline to follow-up was considered to represent a real (biologic) difference. Changes in circulating bFGF and VEGF levels appeared random and no describable, consistent pattern could not identified. In contrast, TNF- α levels increased by \geq 25% in 14 of 21 (67%) informative patients from baseline to week 2. Furthermore, several TNF- α levels continued to increase in several patients. Fourteen of 20 (70%) patients had rising TNF- α levels by \geq 25% and no one had decreased levels by \geq 25% from baseline to week 4. See Figure 1. Of note, the only patient who did not have rising TNF- α levels was the single patient that experienced a near partial response. The precise significance of this observation, if any, is unclear. Pharmacokinetic data are still being analyzed.

Thalidomide Trial Summary. We conclude that thalidomide at 800 mg/day had no detectable activity in this setting. Furthermore, it was only moderately tolerable, mostly due to somnolence

and other neurotoxicities. According to our prospectively written criteria, at least one patient, and perhaps two, failed to progress at 8 weeks on the lower dose. Therefore, thalidomide may have some activity in patients with metastatic breast cancer, but it must be considered minimal, at best. We have elected not to proceed with further accrual, since our conclusion is that the activity of thalidomide in this patient population, if it exists, is too small to justify ongoing administration to patients.

The only discernable trend in angiogenic growth factors was a consistent rise in TNF- α levels after treatment, which incidentally, was not observed in the single patient who experienced a near partial response. Otherwise, the results of angiogenesis assays failed to provide any real insight into why thalidomide was not more active against metastatic breast cancer in this setting. Circulating levels of thalidomide are now being determined to be certain that the pharmacokinetics in this population are not different from those in the normal population. However, it seems unlikely, since drowsiness was observed as expected, and toxicities were greater in the 800 mg/day arm, suggesting that adequate drug levels were achieved. Pilot QOL and cost analyses are discussed in the Core 2 section of this Report.

III. KEY RESEARCH ACCOMPLISHMENTS

- Completed Phase I study of TNP-470 plus paclitaxel
- Completed Phase II study of thalidomide

IV. REPORTABLE OUTCOMES(1-3)

1. Baidas S, Bhagava P, Isaacs C, Rizvi N, Trocky N, Pipkin T, Hayes DF, Chen H, Marshall J. A phase I study of the combination of TNP470 and paclitaxel in patients with advanced cancer. Proc. Am. Soc. Clin. Oncol. 19:205a, 2000.
2. Baidas S, Isaacs C, Crawford J, Winer E, Fleming G, Harris L, Pluda J, Hawkins M, Lippman L, Hayes DF. A phase II evaluation of thalidomide in patients with metastatic breast cancer. Proc. Am. Soc. Clin. Oncol. 18:125a, 1999.
3. Baidas S, Winer E, Fleming G, Harris L, Pluda J, Crawford J, Isaacs C, Hanfelt J, Flockhart D, Johnson M, Yamauchi H, Hawkins M, Lippman M, Hayes DF. A phase II evaluation of thalidomide in patients with metastatic breast cancer. J. Clin. Oncol. 14:2710-2717, 2000.

V. OVERALL SUMMARY: As stated, the overall goals of this project were to evaluate the effects of angiogenic inhibitors in prospective clinical trials in patients with breast cancer. We have now successfully completed a randomized phase I/II study of thalidomide, which has provided insights into the relative lack of activity high dose (800-1200 mg) and standard dose (200 mg) thalidomide.

Furthermore, we have finished a Phase I trial that addressed whether TNP-470 contributes added benefit to the chemotherapeutic agent, paclitaxel.

Although thus far we have failed to observe an apparent efficacy benefit with either of these strategies, these data are of critical importance to the research community. The hypothesis that angiogenesis inhibition will be an effective treatment for cancer continues to be highly controversial, both in the lay and scientific press. Our results suggest that, at least, thalidomide as a single agent is not an effective treatment for metastatic breast cancer. Our study also provides tolerability data for investigators who might wish to pursue high dose thalidomide. These observations may be useful if thalidomide is to be studied either in combination with other agents or in other diseases, such as Kaposi's sarcoma and multiple myeloma, in which some activity has now been reported.

We continue to maintain an interest in TNP 470 and, ultimately and if justified, a randomized trial of this agent with paclitaxel. TNP 470 has remarkable anti-angiogenic activity in pre-clinical models. Rather than conclude that it is not active clinically, we await pharmacokinetic data to determine if drug levels are unfavorable unless TNP-470 is delivered over long periods of time or very frequently. A phase I trial of TNP 470 delivered as a continuous infusion over five days is now ongoing at Lombardi. After completion of this trial, we are considering another phase I trial of the combination of this agent as a continuous infusion with weekly paclitaxel. If the results of that phase I trial are promising, then we will pursue the prospective randomized clinical trial of paclitaxel, with or without TNP 470.

VI. REFERENCES

1. Baidas S, Bhagava P, Isaacs C, Rizvi N, Trocky N, Pipkin T, Hayes DF, Chen H, Marshall J. A phase I study of the combination of TNP-470 and paclitaxel in patients with advanced cancer. *Proc. Am. Soc. Clin. Oncol.* 19:205a, 2000. (reprint included in full packet following annual report text)

ABSTRACT:

TNP-470 [T], a fumagillin derivative, and Paclitaxel [P], a cytotoxic agent, possess potent anti-angiogenic and anti-tumor activity. The activity of T is believed to be mediated via inhibition of the enzyme methionine aminopeptidase-2, while P is a microtubule stabilizing agent. Preclinical data suggest that P may prolong the half-life of AGM-1883, an active metabolite of T, through inhibition of its metabolism. Based on different mechanisms of anti-angiogenic activity and potentially beneficial metabolic interaction, a trial was conducted using a combination of T and P in patients (pts) with advanced, incurable solid tumors. T was administered as a 4-hour iv infusion on day 1; P was started on day 8 as a 1-hour iv infusion, immediately followed by T. Both drugs were administered together weekly for 3 weeks, followed by a 1 week break. Pharmacokinetics (PK) were performed on day 1 and 8. Twenty-two pts were treated: 8M/14F, median age 52 (33-74), ECOG PS 0-2. Primary tumor sites: Breast (5), Lung (5), Ovary (3), Cervix (2), others (7). Number of pts per dose level were: no. of pts (T dose in mg/m²/ P dose in mg/m²): 3 (88.5/70), 3 (88.5/80), 3 (133/80), 7 (133/90), 3 (177/90), 3 (177/100). Preliminary data reveal the following toxicities: fatigue (gr 1), nausea/vomiting (gr 1-2), diarrhea (gr 1-2), hair loss and myelosuppression believed to be due to P. Three pts developed peripheral

neuropathy (gr 1-2), and two pts developed transient ocular scotomas attributable to P. Two pts experienced lightheadedness, and one pt developed decreased memory and difficulty finding words, all of which have been previously observed with T. The median duration of treatment was 15 wks (3 wks to >1yr); 5 pts received treatment for ≥ 6 months. PK data will be presented. A pt with ovarian cancer, who had progressed after P chemotherapy, had a partial remission ($>75\%$ reduction) after 6 months of treatment, and a pt with metastatic breast cancer had a minor response and has received treatment for >1 year. In summary, T and P can be administered together safely up to the maximum tolerated doses of both drugs (177 mg/m^2 of T and 100 mg/m^2 of P), and appear to be an active combination. [T was kindly provided by TAP Holdings Inc]

2. Baidas S, Winer E, Fleming G, Harris L, Pluda J, Crawford J, Isaacs C, Hanfelt J, Flockhart D, Johnson M, Yamauchi H, Hawkins M, Lippman M, Hayes DF. A phase II evaluation of thalidomide in patients with metastatic breast cancer. *J. Clin. Oncol.* 14:2710-2717, 2000.

VII. APPENDIX: Baidas manuscript

CORE 1: PATIENT ACCESSION CORE

I. INTRODUCTION: The overall goal of the Patient Accession Core (PAC) has been to promote and facilitate increased participation, in current and proposed Lombardi Cancer Center Breast Center research protocols, by patients and high-risk women who have historically had difficulty accessing and benefiting from cancer prevention, diagnostic and treatment trials. Two particular groups of patients and high-risk women have been the focus of these outreach efforts: 1) medically underserved populations, particularly African-American and elderly patients and 2) high-risk individuals who are members of health maintenance organizations (HMOs).

During Year 3 of the project, efforts were directed toward meeting the objectives specified for the Patient Accession Core (PAC) of the DOD-funded Breast Cancer Support Grant at the Lombardi Cancer Center. As noted in the Year 2 progress report, the PAC engaged in activities different from those specified in the original proposal. As such, these are reiterated within the discussion of original objectives or in the conclusion of this section. The specific aims of the proposed PAC have been as follows:

- **Expand Lombardi's established links with the community-based Washington D.C. organizations and primary care clinics already serving the needs of the area's medically underserved.** This was done by forming a Community Advisory Board and a Clinic Advisory Board to the Lombardi Breast Cancer Research Center in order to review community-based education, protocol promotion, clinical referral, and patient transportation mechanisms. Our limited minority accrual experience in the first two years of the PAC caused us to modify this approach and subcontract with a social marketing firm (Matthews Media Group) to promote participation in the DOD-funded CARE study, and to a lesser extent the CABCAD study.
- **Expand Lombardi's links with local and national Health Maintenance Organizations (HMO) serving the greater Washington D.C. area.** This was done by forming an HMO advisory board to the Lombardi Breast Cancer Center to review HMO member education, protocol promotion and clinical referral mechanisms and to participate in evaluating cost-effectiveness data from HMO members participating in breast cancer diagnosis and treatment trials at the Lombardi Center. Based on rapid and repeated turnover of Managed Care Organization leadership, making it difficult to negotiate referral arrangements, in the 03-year we began to focus on HMO's with a larger medically underserved patient population.
- **Expand Lombardi's existing breast cancer education materials and health promotion programs** by making them available through the information superhighway (e.g. the Internet) for HMO members and by basing these materials and programs in medically underserved community settings. All LCC protocols are being posted on our Website, and MMG developed CARE promotion materials that were disseminated through primary care clinics, HMO's and community organizations.
- **Provide cultural awareness and sensitivity training to Lombardi Breast Cancer Center clinicians** involved with prevention, diagnostic and treatment research

protocols to ensure supportive patient care for all patients on clinical trials. Two training sessions were held in Year 2.

- **Provide free transportation**, with the Lombardi Cancer Center van, for medically underserved patients for whom transportation to, and/or parking in, Georgetown may represent a barrier. Accrual has been so limited that this issue did not arise.

II. PROGRESS REPORT: The following represent major accomplishments of the Patient Accession Core during Years 1 through 4:

A. Community Outreach Initiatives

Community Advisory Board (CAB): During Year 3, the Community Advisory Board was not reconvened, based on the lack of referrals being generated by member organizations during the first two years. During the two meetings held in Year 2, CAB members were alerted that the PAC would be contracting with an independent company to support the patient recruitment efforts for clinical research. Lenora Johnson, the PAC coordinator, solicited potential candidates for the contract at that time. CAB members were also informed of the PAC plans to offer training workshops in cultural awareness and sensitivity to LCC staff members working with patients in clinical trials. An overview of the training workshop was shared with members of the CAB.

Primary Care Clinic Advisory Board: Just as with the CAB, the Primary Care Clinic Advisory Board was not reconvened during Year 3. For community-based primary clinics there have been two paramount challenges to recruitment. The first was our inability to provide services to Spanish speaking populations (two of the clinics on the board provide health services to Hispanic communities) and the second was developing efficient referral methods for clinic clinicians.

In response to the concern for meeting the needs of Hispanics, PAC worked with Dr. Caryn Lerman on a proposal to broaden the range of the CARE program by procuring a bilingual genetic counselor and the capacity to provide CARE services off site in community settings. All of the clinics belonging to the PAC advisory board submitted letters of support for that proposal and it was funded. While identifying a bilingual genetic counselor was difficult, clinic board members had felt it was necessary that women whose native language is Spanish should be counseled in the Spanish language. The Cancer Genetics Network support made this possible, however resources for Spanish-speaking patient accrual only recently were put in place. A recent cooperative agreement grant application submission to the National Cancer Institute, with the Washington Hospital Center and five primary care clinics serving D.C.-area Hispanics, may provide five years of financial support to continue and extend the DOD Breast Cancer Research Center efforts to involve this hard-to-reach population in breast cancer research.

B. HMO Advisory Board: PAC staff members redirected their approach in Year 3 to reaching managed care organizations with a large medically underserved (Medicaid) population. During Year 2 PAC staff had met with Linda Meili, RN, MS, ONC, Coordinator for Managed Care Programs, then at the LCC and Patricia Robinson, Senior Account Manager, Managed Care Department - GUMC. It was believed that a cooperative strategy for reaching

managed care organizations would prove more successful. Also, given the legislative attention relating to broadening opportunities for managed care membership participation in clinical research trials, it was believed that the provision of an informational session (seminar, presentation, symposium) for leaders of area managed care organizations may be of interest. PAC staff would continue to work with LCC and GUMC staff to develop and implement effective ways of reaching out to the dynamic managed care system.

During Year 3, Dr. Kerner met with Cecile A. Comrie, Associate Director for Health Education and Wellness for the D.C. Chartered Health Plan. With 25,000 D.C. Medicaid participants, Chartered represents the largest Medicaid Managed Care Organization in the D.C. region. The enrollee population is almost exclusively African and Latin American. MMG made the initial contact with Chartered, and set up a system to have the five Chartered outreach workers collect family history of breast or ovarian cancer during their regular family visits. Started in March 1999, this system produced approximately 90 family history forms turned in over a six-month period. This volume was well below the daily number of family visits conducted by Chartered (n=60). Moreover, fewer than five of the families for whom history forms were collected were found to be eligible for inclusion in the DOD-supported CARE study.

Chartered then requested more health education information about genetic testing and counseling for its members, and also requested some form of incentive payment for its outreach workers when they find eligible patients. In response to these requests, the LCC Division of Cancer Prevention and Control health education staff met with Chartered Health Education staff to plan new health education programs for Charter members on genetic testing and counseling for breast cancer. In addition, we included a \$50 incentive payment in the Year 4 budget to Chartered for each patient enrolled on a designated Breast Cancer Research Center study, up to 150 enrollees. Despite our best efforts, few patients were referred.

Breast Cancer Education Plan: It was originally intended that the Breast Cancer Resource Committee (BCRC) would develop and promote a campaign around the topic of clinical trials participation for African American women. As discussed in the last annual report, half way through Year 2, BCRC decided that it would not be in their best interest to enter into a contractual agreement with LCC. As such, PAC released a Request for Proposals to identify another provider for this service, and awarded the subcontract to Matthews Media Group, Inc. (MMG) located in Rockville, Maryland. MMG had a successful history of recruiting patients to clinical research trials through their interactions with the National Cancer Institute and other sites including:

- Area C Chest Clinic
- Arlington County Chest Clinic
- Community for Creative Non-Violence Clinic
- D.C. General Hospital
- *La Clinica del Pueblo*
- *Spanish Catholic Center*
- Upper Cardozo Community Clinic
- *Woodridge Neighborhood Clinic*
- *Zacchaeus & Bread for the World*

The italicized clinics were those already represented on the PAC Clinic Advisory Board.

Monthly meetings were set up between MMG, PAC and CARE study staff. During these meetings, MMG reviewed their social marketing approaches to outreach and education of D.C. Region African American populations. MMG focused their recruitment efforts on the CARE protocol, with a target of 100 eligible patients within Year 3 - MMG was unable to achieve this goal. Based on the barriers identified by MMG and the CARE study's more successful experience with focusing its recruitment in oncology practice settings, LCC and MMG mutually agreed to end the MMG subcontract at the end of Year 3. At LCC's request, MMG provided the PAC with a Final Project report that outlined the barriers faced and the lessons learned from the one-year MMG experience. A copy of this report was included in the last annual report.

C. Cultural Awareness Training: Education For Quality Living (EQL), an agency based here in Washington DC, conducted a focus group and a series of in-depth interviews in Year 2 to obtain data which would enable them to tailor an existing workshop to the specific needs of LCC staff members. That data was compiled and reported on (poster presentation) at the Cancer and Literacy conference offered by the Moffitt Cancer Center in Florida on April 30, 1998. The results were appended to the Year 2 progress report.

The *Culture & Health* workshop was offered as a pilot to 12 staff members in June 1998. PAC staff worked with EQL to revise the workshop based upon feedback of this workshop in preparation for a September 1998 workshop. The major changes included a focus on research staff members and greater input from participants with respect to their personal experiences with cancer rather than depend on EQL for that input. No additional workshops were proposed or held in Year 3.

D. Patient Transportation Support: Originally, the plan was to utilize the Lombardi Cancer Center van to pick up a group of patients at their referring hospital or clinic site. The logistics of such an endeavor were complicated in that the CARE and CAB/CAD studies require two to four hours of time for each individual to complete their sessions, and only one woman may attend a counseling session or receive diagnostic testing at one time.

To address transportation barriers, alternate mechanisms were put in place for provision of parking and taxi vouchers. It was expected that many of the women referred from the primary care clinics to the CARE and CAB/CAD studies would need to take taxis to get to Georgetown. A system is already in place, for the CAB/CAD study, where women who need to take a taxi are identified during the intake session over the telephone and asked to call a taxi service under contract with Georgetown University Medical Center. When the patient arrives at Lombardi Cancer Center, the project coordinator for the study meets her taxi and provides the driver with a voucher. Likewise, when the patient leaves to go home, a taxi is called and a voucher is provided.

E. Additional Patient Accrual Efforts

Lombardi Extramural Research Consortium (LERC): During the first year of the PAC, additional recruitment efforts were developed at the recommendation of the senior investigators and the Cancer Center's administration. The most intense effort was the coordination between the PAC and the LCC Extramural Research Consortium (LERC). LERC was designed to provide community-based oncology practices the opportunity to deliver research protocol care from a community office setting. As such patients wishing to be considered for a research study

could have the protocol care delivered in the comfort of their own oncologist office practice, without having to travel into Georgetown. The LERC committee met on a monthly basis, to evaluate new protocols where the LCC PI has requested LERC accrual, and to review accrual, data collection and data management performance of the individual office practices.

This committee originally consisted of two representatives from PAC, Dr. Jon Kerner (Associate Director for Prevention and Control) and Lenora Johnson (Senior Health Educator), Dr. John Marshall (Associate Director for Extramural Research, Clinical Research Management Office and Associate Professor of Medicine), and Jan Hewitt (Sponsored Clinical Research Coordinator). This group met monthly with the LERC staff (1 FTE nurse, 1 FTE data manager) to coordinate efforts to increase research referrals from external sources; namely oncology physicians' practices. The activities of this group:

- secured funding from the Lombardi Cancer Center to provide additional support for extramural research activities from the Director's shared resources allocations;
- conducted focus groups among local community and private practice oncologists and surgeons to identify barriers to partnering for the purpose of clinical trial recruitment; and
- developed protocol-specific patient information sheets for all community-based cancer patients that were considered for accrual to LCC clinical trials open to LERC physicians.

The LERC successfully established a network of four D.C. and three Virginia community office practices which accrued 36 cancer patients (19 breast cancer patients) from July 1, 1998 through June 30, 1999. One of these practices has a relatively large number of Hispanic patients, but none to date have had a significant number of African American patients. Based on the relatively good patient accrual experienced by LERC, in relation to the community outreach and social marketing approaches, Dr. Kerner and Dr. Marshall merged the resources of the LERC and the PAC into the Lombardi Education And Research Network (LEARN). The mission of LEARN is:

- to expand the network of community-based oncology practices that accrue patients to LCC clinical trials, with a targeted effort to add community practices that have a significant number of African American and/or Latin American patients;
- to educate community physicians and their patients about the benefits of participating in new LCC protocols as they are reviewed and approved by the LCC Clinical Research Committee, the GUMC Institutional Review Board, and the LEARN steering committee; and
- to educate LCC physician investigators and research staff about how best to recognize and reinforce community physician and patient involvement in LCC clinical trials.

The LEARN activities: 1) support existing oncology office practices in expanding their breast cancer patient accrual to LCC clinical trials; 2) identify and recruit new community office or hospital-based oncology practices to join LEARN; 3) work with LEARN practices to network out to their referring surgeons and internists to identify those interested in participating in LCC breast cancer prevention and early detection trials; and 4) work with targeted managed care

organizations to get their affiliated physicians to participate in LEARN. Long-term support for these activities will be based on the success of the LEARN expansion, the number of new and minority patients going on protocol, and the resources collected from sponsored research to which LEARN makes a significant patient accrual contribution. At this time, these activities have been somewhat limited due to the shortage of research nurses at GUMC.

Community Hospital Partnerships: PAC staff communicated with the Providence Hospital (NE Washington, DC) for more than 18 months for the purpose of working through a process for collaboration in clinical research studies. These communications had a limited impact, and despite our best efforts and persistence, no agreement was ever reached.

Finally the PAC obtained a listing from the Maryland Tumor Registry of the ten Maryland hospitals that served the largest number of African American breast cancer patients in the state. Of the hospitals treating the 110 breast cancer cases in Montgomery and Prince George's counties in 1995, Prince George's Medical Center and Doctor's Hospital in Prince George's County treated the most patients. In Year 4, these hospitals were to be approached by the LEARN Project Coordinator. Unfortunately, as mentioned above, the lack of dedicated nursing staff prevented this from being completed.

Physician Practices: PAC developed a database of all oncologists and oncology surgeons in the Washington Metropolitan Area. The list is approximately 250 members in size, which includes multiple offices of a single practice. A letter was mailed to these practices that addresses referrals to clinical trials. A brochure that briefly explains clinical trials accompanied the letter along with the materials already developed and produced for each of the three Breast Cancer Research Center protocols. Twelve physicians responded with an interest in collaborating with GUMC for the purpose of collaborating in cancer treatment trials. Some of these practices have subsequently joined LEARN.

III. KEY RESEARCH ACCOMPLISHMENTS: Not Applicable

IV. REPORTABLE OUTCOMES: Despite considerable effort by the PAC staff to implement the minority patient recruitment plan, through extensive meetings and collaboration with the Community Advisory and Clinic Advisory Boards, and subcontracting to MMG the level of minority patient accrual, to date, has been less than anticipated.

The tables below represent accrual figures for Years 1-3 for the prevention and diagnostic studies.

Table 1. Accrual Data for CARE Study

Racial/Ethnic Group	Year One		Year Two		Year Three		Year Four	
	Baseline Only	Baseline & Educ.	Baseline Only	Baseline Only	Baseline & Educ.	Baseline & Educ.	Baseline Only	Baseline & Educ.
African American	12	7	7	3	10	10	3	5
Caribbean or West Indian	0	0	1	0	2	1	0	0
White/non-Hispanic	218	161	162	114	337	327	31	187
Hispanic	1	1	2	2	6	4	0	1
Asian or Pacific Islander	1	1	1	1	2	1	0	2
Native American	0	0	1	1	1	1	0	0
Other	1	1	4	2	3	2	1	3
Unknown	1	0	0	0	0	0	0	1
Total	234	171	178	123	361	347	35	199
Total Minority Accrual	15 (6.4%)	9 (5.3%)	16 (9.0%)	9 (6.9%)	24 (6.6%)	20 (5.8%)	4 (11.4%)	12 (6.0%)

Table 2. Accrual Data for CABCAD Study

Racial/Ethnic Group	Year One	Year Two	Year Three	Year Four
White/non-Hispanic	46	80	37	22
African American	4	6	4	7
Hispanic	0	1	0	1
Asian or Pacific Islander	2	2	0	2
Other	1	1	0	1
Unknown	0	0	19*	0
Total	53	90	60	33
Total Minority Accrual	7 (13.3%)	10 (11.1%)	4 (6.7%-10.8%)*	11 (33.3%)

*Depending on adjustment for missing race data.

V. CONCLUSIONS: Based on an analysis of this experience, and a review of other successful and unsuccessful efforts at minority clinical trials accrual, the LCC proposed to expand minority accrual to breast cancer research trials by expanding an existing network of oncology office practices, and their affiliated internist, ob/gyn and surgical practices. We focused on recruiting office practices that have a large minority patient population. In this manner, we tried to build on-going relationships where patients could be treated on protocols locally, and the trust and understanding engendered among community physicians and patients by the LEARN program could improve referral to Georgetown protocols where such referrals are necessary. Unfortunately, our efforts were less than successful. Therefore, in August 2000, we requested and obtained approval to reallocate these funds to provide web-based infrastructure for clinical trials information. We have included the text from the letter of request below:

“This letter is to inform you that Dr. Jon Kerner, Principal Investigator of the Patient Accession Core (PAC) of the referenced contract, left the Lombardi Cancer Center in April 2000, after he was recruited by the Chemoprevention Branch of the National Cancer Institute. We are requesting to name Dr. Lippman as the PI of this Core.

During his time devoted to the activities of the PAC, Dr. Kerner made great progress, as outlined in the Year 3 Progress Report (October 1999). As reported, considerable effort was devoted to implement the minority patient recruitment plan, through extensive meetings and collaboration with the Community Advisory and Clinic Advisory Boards, and subcontracting to Matthews Media Group. Despite these efforts, the level of minority patient accrual has been less than anticipated.

Based on an analysis of this experience, and a review of other successful and unsuccessful efforts at minority clinical trials accrual, the LCC has attempted to expand minority accrual to breast cancer research trials. We expanded an existing network of oncology office practices, and their affiliated internist, ob/gyn and surgical practices. Focus was given to recruiting office practices that have a large minority patient population. In this manner, on-going relationships continue to be built where patients can be treated on protocol locally. In addition, the trust and understanding engendered among community physicians and patients through our programs will ultimately improve referral to Georgetown protocols, where such referrals are necessary.

In the Year 4 budget already approved, we requested to increase the percent effort of those involved in these activities. However, given Dr. Kerner's departure, we are now requesting to reallocate these funds to provide web-based infrastructure for clinical trials information. This will ultimately allow us to build accrual, and to expand the standard clinical trials' information base. By working to enhance our existing Lombardi Cancer Center web site, we will improve web communications for patients and for referring physicians. We plan to provide potential participants and their physicians with the latest information on available trials and modifications, along with the ability to search the site for appropriate trials – trials that are explained in a format understandable for patients. One of the barriers identified to participation in clinical trials is the time required to explain the entire issue of clinical trials, and then the specifics of individual trials to potential participants. We anticipate that the enhancement of our web site will help to overcome this barrier, by providing an explanation that can be reviewed by the patient before meeting with the physician.

The cancer center has an established contract with Results Direct, Inc. which helped us design a new site, and which continues to host and maintain the active Lombardi Cancer Center site. We are currently working with this company to develop additional interactive pages, specifically targeted to breast cancer patients and referring physicians.

Up until April 2000, the funds awarded to the PAC were being spent as approved in the revised Year 4 budget. Following Dr. Kerner's departure in April 2000, we continued to spend the additional salary support funds through June 2000, the end of that current fiscal year. The additional funds allocated to travel, materials, and other expenses have not yet been spent. Therefore, we are respectfully requesting to rebudget the funds remaining in the PAC, approximately \$68,000 in direct costs (April through August 2000), to the activities described above. The revised five-month budget has been attached for your review and approval.”

We continue to work with Results Direct, Inc., the contractor hired to maintain the LCC website, and our Clinical Trials Management Office, to enhance the website to meet the following goals:

- Work closely with Results Direct Inc. to develop and maintain the site in order to increase accrual with web-based information about clinical trials and specific protocols; identify a dedicated member of the Clinical Research Management Office to be responsible for the ongoing update of clinical trial information.
- Make material available in PDF format so that hard copies can be used by all users; protocol information may be printed and placed on display in waiting rooms, etc. ; many patients first hear about clinical trials only after being diagnosed.
- Provide a SEARCH function so that patients/physicians can search by cancer type, stage, treatment modality, and protocol number ; more patients are using the Internet to get their information and to seek the latest treatments.
- Facilitate accrual by allowing potential participants to review material before and/or after meeting with physicians; this will save the physician and staff time explaining trials---a barrier to participation.
- Make available basic clinical trials information on the website, e.g., why potential participants may be interested, etc., further saving physicians time explaining the process.
- Provide latest information and modifications of all trials available at Lombardi, contact information, and logistical information, e.g., transportation and other services available, maps, parking, etc.; E-mail and phone numbers for the contact of each trial.
- Make available this material which will be appropriate for potential participants, as well as LCC physicians, community physicians, social workers, state health district staff, and advocacy organizations --- more widespread dissemination throughout the region...one format to be used by many.
- Enhance ability for potential participants to discuss and inform family and friends about clinical trials and possible participation; cancer patients most often seek advice from influential people in their lives.
- Provide publicity about latest treatments, Lombardi trials; Lombardi researchers can direct interested people to the website for further information.

VI. REFERENCES: Not Applicable

CORE 2: CANCER CLINICAL AND ECONOMIC OUTCOMES CORE

1.0 INTRODUCTION: Over the course of the Breast Cancer Center Grant the Cancer Clinical and Economic Outcomes Core (hereinafter referred to as the "Outcomes Core") constituted a multi-disciplinary research team (including oncology, nursing, primary care, economics, health services research, psychology, and biostatistics) with broad methodological expertise to conduct evaluations of the costs and outcomes of the new translational technologies. The Outcomes Core has completed evaluations of the three projects included in this Breast Cancer Center grant. As evidence of the overwhelming success of the Core and its contributions to research across the Cancer Center, the Outcomes Core will be included in the next competing continuation of our National Cancer Institute-funded Cancer Center Support Grant.

Scope of the Outcomes Core Research: The overarching mission of the Outcomes Core is twofold: 1) to expand the technical capacity for outcomes evaluations for current and future research at the Lombardi Cancer Center; and 2) to provide expertise and support to the research projects included in the Breast Cancer Center. The Core technical aims are listed below:

1. To conduct cost-effectiveness analyses (CEAs) of each of the projects.
2. To evaluate the impact of tests or treatments on quality of life (QOL).
3. To evaluate the impact of the other Center Core, the Patient Accession Core (PAC).
4. To develop a centralized library of data for use in cancer outcomes research, and provide consultation to investigators on outcomes assessment for new initiatives.

2.0 BODY: The Outcomes Core evaluations were done in a coordinated manner across all projects, but for the sake of clarity of presentation, the progress applicable to each project are presented separately. Table 1 presents an overview of our approach for each project. The narrative that follows highlights final results.

Table 1: Overview of Project Specific Outcome Evaluations

	Project #1: Prevention: Genetic Testing	Project #2: Diagnosis: New Technologies	Project #3: Treatment: Novel Palliative Rx
Design	Observational Cohort	Case Series	Phase I, II studies
Outcomes	QOL, Utility, QALYs	Patient Satisfaction; Costs	QOL, Utility
Costs	Direct and Time Costs	----	----
Economic Analysis	CEA Model	----	----

2.1 Project #1: BRCA1/2 Genetic Testing: Conduct a Cost-Effectiveness Analysis (CEA), Combining Primary and Secondary Data, to Identify the Key Parameters Which Drive the Costs and Effectiveness of Genetic Testing and Counseling as a Strategy to Prevent Breast Cancer and Decrease Cancer Mortality among High-Risk Women: We have completed three products for this aim: one published paper and two manuscripts submitted to peer-reviewed publication.

2.1.1 Women's Preferences for Testing Outcomes: Women deciding whether to partake in genetic counseling and testing, and women who test positive who have to decide on management options must weigh the risks and benefits of their choices. Women who have chosen to undergo testing have been reported to be quite variable in their rates of undergoing prophylactic surgery to reduce risk of breast and ovarian cancer (Lerman, 2000; Meijers-Heijboer, 2000). In order to choose a management option, women must implicitly or explicitly decide about their preferences for the outcomes associated with each option, including the quality of life of living with the results of the management option (e.g., having both breasts and/or both ovaries removed), and the resulting risk of cancer and the associated quality of life of living with breast or ovarian cancer.

To evaluate preferences for these different potential outcomes, we studied a group of women at high-risk for having a BRCA1 or BRCA2 mutations. The results of this study are summarized in the manuscript included in Appendix 1 (Lawrence et al, 2001). Briefly, participants included 587 women enrolled between 1996 and 2000 in a longitudinal study of people at high-risk of having a breast cancer susceptibility mutation. Women were eligible if they had at least a 10% prior probability of carrying a BRCA1/2 mutation, determined based on combinations of age, breast and ovarian cancer status, family history of breast and/or ovarian cancer, and race (i.e., Ashkenazi Jews) (American Society of Clinical Oncology statement, 1996). In addition, women who were relatives of a person known to be BRCA1/2 positive were eligible.

After providing written informed consent, data were collected on family history, medical history, risk factors, and psychological well-being during enrollment and follow-up computer assisted telephone interviews (CATI). Preferences, or utilities were measured using the Health Utilities Index (HUI) 16Q, time-trade-off hypothetical scenarios (TTO), and a linear rating scale (LRS). TTO assessments were discontinued due to reported high patient burden and poor reliability. The HUI measures domains of sensory perception, pain, mobility and dexterity, emotional function, cognitive function, self-care, and fertility. This instrument has been validated, and has been able to show differences between breast cancer patients who have had mastectomy and breast conserving surgery (Feeny et al., 1996). The HUI scores were calculated using the HUI Mark II algorithm (Torrance et al, 1996).

Pearson's correlation coefficient was used to compare utility measures and to assess test-retest reliability. T-tests were used to examine the influence of age, breast cancer status, ovarian cancer status, and BRCA mutation status on utility scores. Finally, a multi-variate generalized linear model was used to examine the relative importance of age, cancer status, mutation status, and current health on utility results. Test-retest reliability for the LRS was 0.75.

Of note, women rated the utility of early breast cancer quite high, in the range for their assessments of their overall current health. Women also rated the utility of having mastectomy, breast conserving surgery, or prophylactic mastectomy similarly. Women rated having an in-breast recurrence somewhat lower than having early stage disease, and, as expected, ranked metastatic disease fairly low.

One of the major determinants of the utilities for early breast cancer was whether or not the participant had breast cancer. For example, controlling for other covariates, those with breast cancer rated the health states involving early breast cancer 6 to 10 points higher than those without cancer. Of note, among cancer and non-cancer patients, ratings of life with a lumpectomy, mastectomy, and prophylactic mastectomy were similar. Women who tested positive for BRCA1 or BRCA2 susceptibility genes also tended to have higher utilities for their health and for mastectomy compared to those without mutation. The average utility for each health state before the disclosure of genetic testing results did not differ significantly after results were given.

Based on these results, we concluded that women with BRCA1/2 mutations will need to consider several factors in deciding on surveillance or prophylactic surgery, including trade-offs between short-term quality of life and the long-term risk of future cancer, and the health related quality of life associated with these cancers.

2.1.2 Costs of Genetic Counseling and Testing: A large portion of the costs in this cost-effectiveness analysis will be the costs of providing genetic counseling and testing of women who are at risk of having a mutation. Our assessment of the costs of genetic testing and counseling were recently published (Lawrence et al, 1999). This publication is included in Appendix 1. Briefly, we used data from Project 1 in a micro-costing analysis to summarize the time and effort required for a genetic counselor to provide counseling (and full BRCA1/2 gene sequencing), and for women to receive this service. This analysis included the cost of the personnel time, materials, and included participant time and caregiver costs. The cost of providing standard genetic counseling (without testing) to probands was \$213; adding testing and disclosure of results to this counseling increased total costs to \$2057. While the cost of counseling and testing together exceeded \$2000, the cost of providing the counseling (including disclosure of results) comprised only 16% of the total cost. We conclude from this analysis that: 1) counseling is an important part of a genetic evaluation and has a low cost relative to testing; and 2) since the cost of counseling is a small part of the overall cost of counseling and testing, replacement of detailed genetic counselor counseling with a shorter time of physician counseling would not significantly lower costs.

2.1.3 Cost-Effectiveness of Counseling and Testing for BRCA1/2 Mutations: We created a mathematical stochastic simulation model to extend the analysis time horizon beyond the period of observation in Project 1 and calculate the costs and outcomes of offering genetic counseling and BRCA1/2 testing to women at risk of carrying a susceptibility mutation, compared to offering counseling only, and to routine medical care. The results of this portion of the project are presented in the manuscript included in Appendix 1 (Lawrence et al, 2001). Briefly, the model portrays the process of care from initial counseling and testing, all downstream costs of and effects of all

possible events that flow from the initial testing choices, through death from breast or ovarian cancer or other causes. The results are presented in incremental cost-effectiveness ratios, with costs expressed in dollars and effects expressed as life years (LYs) and quality-adjusted life years (QALYs). We used a societal perspective in the analysis. Based on the results of the model, we conclude that the costs-effectiveness of offering genetic testing and counseling is highly dependent on pre-test probability of having a mutation, so that is it only cost-effective to provide this service to women at the highest levels of risk. Cost-effectiveness is also dependent on the age of offering screening and the proportion of women who elect prophylactic mastectomy and oophorectomy. For instance, testing and counseling an 18 year old woman with very high risk, and who elects removal of both breast is about \$27,000 per year of life saved, while testing and counseling a 45 year old women increases to almost \$43,000 per year of life saved. Lower prevalence of susceptibility mutations increase the cost-effectiveness ratio (i.e. make counseling and testing less cost-effective), but if more women who test positive for a mutation choose prophylactic mastectomy to manage their cancer risk, counseling and testing become more cost-effective.

2.2. Project 2: Coordinated Approach to Breast Cancer Diagnosis: Technical Aim: Conduct an economic evaluation of new breast cancer diagnostic evaluation strategies and assess test-related patient Satisfaction: The goal of Project 2 was to evaluate the accuracy of simultaneously administered new diagnostic technologies, including digital mammography, magnetic resonance imaging (Gd-DTPA enhanced MRI), nuclear medicine evaluation (Tc-99m-sestamibi scanning), special ultrasound evaluation (radio frequency elastography imaging), and nipple aspirate fluid (NAF) cytology via correlation with pathological results of surgical excisional biopsy. There were two outcomes objectives associated with Project 2 - cost-effectiveness of interventions and patient satisfaction. Unfortunately, the technologies studied in Project 2 have lacked sufficient sensitivity to be able to sufficiently rule out cancer in women who have an abnormal mammogram or clinical breast examination; therefore, investigators have concluded that the diagnostic interventions studied are ineffective, precluding a cost-effectiveness analysis. Therefore, this portion of the report focuses on the second objective - evaluating patient satisfaction. The full results are presented in the manuscript included in Appendix 1 (Liang et al, 2001).

Briefly, for the satisfaction evaluation, we used data prospectively collected in Project 2 from a cohort of white and African-American women who had an abnormal breast physical examination, mammography, and/or standard sonography results and had been recommended to have a breast biopsy. After signing the consent form, participants received the diagnostic tests during the one-day clinic visit. A short self-administered questionnaire about satisfaction and acceptability of the tests was given to women by the project coordinator after completion of all tests. Women were also asked to provide their age, monthly household income, medical history (previous breast biopsy, benign breast disease, breast cancer, family history), and women's perceived chance of getting breast cancer in the future. Satisfaction with the diagnostic tests was measured using a modification of the Medical Outcomes Study Visit Rating Questionnaire (Rubin et al, 1993). The six item satisfaction scale used a five point Likert scale to measure satisfaction with the receipt of the tests, the technical skills of the staff, the personal manner of the staff, the convenience of getting the tests, the length of time spent waiting for the tests, and

the explanation of what was done for the participants. Discomfort associated with having a routine mammogram was measured using a 5-item Likert scale (extremely, very, somewhat, mildly, and not uncomfortable at all). To provide a relative standard, we asked the participants to rate discomfort of experimental diagnostic tests compared to having a routine mammogram (a lot less, a little less, no different, a little more, a lot more). Embarrassment was measured using a 4-item Likert scale (extremely, somewhat, mildly, and not embarrassing at all) for all tests. Finally, the willingness to pay (WTP) technique was used to assess women's preferences for having one of the diagnostic tests compared to a surgical biopsy. The WTP questions ask respondents how much money they think women like themselves would be willing to pay out-of-pocket to avoid a biopsy by having one of the alternative diagnostic tests. Two WTP scenarios were used. The first asks about willingness to pay to have a test instead of a biopsy, if the test were as accurate as a biopsy at diagnosing cancer; and the second asks about WTP if the test were nearly (95%) as accurate as a biopsy. We asked participants to imagine whichever test they would most prefer having, to avoid the respondent burden of asking about each test separately. Thus, the assessment provides the maximum the respondent would be willing to pay for any of the tests. Since the WTP technique is sensitive to economic status, WTP was further defined as the amount a woman thinks women like her would be willing to pay as a proportion of the respondent's household income.

A total of 106 patients were recruited for this study, 82 (77%) of whom completed the satisfaction questionnaire. Those who completed and did not completed the survey were similar with respect to demographics and medical history. The mean age of 82 participants was 51.6 (S.D.=10.2, range=25-78), 80% were white, and 14% were African Americans. The majority were high income (income level of >\$3,000). About 46% (n=37) of the women had previous breast biopsy.

In general, participants were very satisfied with the process of receiving different diagnostic tests. For instance, the 79% of women rated their overall satisfaction with the visit for the tests as excellent. The only category of satisfaction that was rated in a lower range was that of satisfaction with the convenience of coming to Georgetown for the tests (only 43% reported their satisfaction with the convenience as excellent). Overall, on a scale from 0 to 100, where 100 represents the highest possible satisfaction score, the mean score was 95.8 (S.D.= 7.64).

About 1/5 of the participants reported that a routine mammogram made them very or extremely uncomfortable, and another 1/5 reported that it did not make them uncomfortable at all. Among those receiving each test, 47% of those receiving MRI, 50% of those receiving digital mammography, and 66% of those receiving sestamibi imaging found the procedure more comfortable than a routine mammogram. Overall, compared to routine mammography, the nuclear medicine test was perceived as the most comfortable test. Embarrassment in undergoing the alternative diagnostic procedures was very low.

Under conditions of accuracy equal to a biopsy, the 43 women who provided a response to the WTP items were willing to pay an average of \$611 to have an alternative test to avoid a biopsy (range \$0-\$10,000), with 7% of women not willing to pay any money out of pocket. Under the scenario where the alternative diagnostic tests were only 95% accurate in diagnosing breast cancer compared to the biopsy, the amount women were willing to pay to avoid a biopsy

significantly decreased to an average of \$308 (range \$0-\$3,000), with 33% of women not willing to pay any money ($p < 0.0001$). This decrease in WTP with accuracy persisted after controlling for patient characteristics, although women ages 60 and older were generally less willing to pay out of their pockets to avoid a biopsy. Interestingly, women who had a previous biopsy (with benign results) were willing to spend more to avoid a biopsy, while women with a personal or family history of breast cancer were less willing to pay to avoid a biopsy.

2.2.1 Serendipitous MRI Results: During the course of Project 2, a number of lesions were noted serendipitously on MRI that were not visualized on the index abnormal mammogram. Since clinicians were concerned about the relevance of these lesions and their probability of being cancer, we constructed a decision model to estimate the probability that these serendipitous lesions were benign if the initial lesion was found to be benign. These results demonstrated that, under our baseline assumptions about the diagnostic accuracy of MRI and mammography, the probability of a lesion being malignant was extremely low. For instance, assuming sensitivity and specificity values of 95.6% and 68.6%, respectively, approximately four of one thousand 55- to 59-year-old women with serendipitous lesions would be expected to have cancer (positive predictive value = 0.44%). We concluded that immediate biopsy of such serendipitous lesions found on breast MRI would not be required. The paper was featured in the Journal of the National Cancer Institute and accompanied by an editorial (Appendix 1).

2.3 Project 3: RCTs of Novel Palliative Treatments for Metastatic Breast Cancer:

Project #3 enrolled a small number of white and African-American men and women for a phase I trial of TNP-470 plus paclitaxel in metastatic cancer, in preparation for a phase III trial in metastatic breast cancer. The Outcomes Core provided descriptions of quality of life (QOL) of trial participants; since this trial has accrued limited numbers, the QOL data should be considered as preliminary and could guide the selection of measures for a phase III trial. In addition, due to the limited accrual and the restriction to a phase I trial, it was not feasible to reliably describe the quality-adjusted survival and costs per unit of clinical outcomes associated with these therapies.

The QOL data have been reported in the ASCO Proceedings (see Appendix 1), and will be included in the manuscript on the clinical trial. Data were collected from 21 patients with metastatic cancer, including the FACT-G, a cancer-specific health profile survey, the HUI (Feeny, 1996), a health utilities index providing societal preference for health, and a LRS assessment, a holistic assessment of a participant's preference for her state of health. We also measured the Rotterdam Symptom Checklist (de Haes, et al., 1990), which provides a listing of possible symptoms.

The HUI scores averaged 0.77 across all patients at baseline (range 0.43-0.95, s.d. 0.15), where zero represents death and 1.0 perfect health. There was no significant change in the HUI scores over the maximum of 8 weeks that the respondents were enrolled in the study. The LRS scores averaged 0.60 (range 0.35-0.90, s.d. 0.16), and did not significantly change while on therapy. The average FACT-B score for the entire study was 77.0 (s.d. 13.7), on a scale scored from 0 (worst functioning) to 148 (best functioning). There was a trend toward a decrease in score between baseline and the average of the on therapy scores, with an average decrease of 3.4, but this trend was not statistically significant ($p = -.35$ by signed rank test).

2.4 Develop a Centralized Library of Data for use in Cancer Research on QOL, Utility, and Cost Measurement Tools and Approaches, and Provide Consultation to Investigators on the Incorporation of Such Tools into New Research Initiatives: The development of this comprehensive cancer outcomes library occurred over the entire four years of the project and has been a valuable resource to cancer center researchers. The library contains reviews of more than 30 breast cancer QOL instruments. Samples of completed reviews for selected tools and a comprehensive bibliography are included in Appendix 2.

2.4.1 Consultations: In the last year of the grant we provided several consultations to Lombardi investigators on the use of outcomes measures in cancer research. One example of a successful consultation included the funding of a project exploring methods to measure the quality of life for patients and caregivers at the end of life. In other consultations, the Core has contributed to seven additional newly funded grants.

2.4.2. Outcomes Core Meetings: The Core has continued to meet regularly over the course of the project, and will continue to meet after the grant ends. The Outcomes Core seminars focus on discussions of current activities and potential new directions.

2.4.3 Grant Submissions: The Outcomes Core members have contributed to, or have been the lead investigators for 13 newly funded peer-reviewed grants that highlight cancer clinical and/or economic outcomes evaluations.

2.4.4 Assess the Impact of the Patient Accession Core: Based on the difficulty in attributing new minority accrual to the Patient Accession Core (PAC), and the closure of this Core, we were not able to evaluate the costs per new patient accrual through the PAC.

3.0 KEY RESEARCH ACCOMPLISHMENTS

- ◆ **Utilities:** In our examination of the utilities, or preferences, of women for the downstream consequences of testing and counseling for BRCA1/2, we found several interesting results. First, among women with high risk for a mutation, cancer patients rated cancer health states higher than the non-cancer patients did. Also, there were no significant differences between women's ratings of lumpectomy, mastectomy, and bilateral prophylactic mastectomy for early breast cancer. Based on these findings we conclude that women re-adjust expectations after a cancer diagnosis, and that treatment choices are equivalent, and should be made based on shared-decision making that considers an individual woman's preference.
- ◆ **Costs of BRCA1/2 Counseling and Testing:** The costs for genetic counseling are low relative to the costs involved in BRCA1/2 testing. Thus, findings derived from cost analyses in this research setting suggest that, in clinical practice, replacement of comprehensive genetic counselor counseling with a shorter time of physician counseling would not significantly lower overall costs.

- ◆ **Cost-Effectiveness of BRCA1/2 Counseling and Testing:** Screening women with a high prior probability of having a mutation is cost-effective by current standards; screening low risk women is fairly costly per year of life saved. The ultimate cost and benefits of testing in general practice will depend on mutation probability and the rate of use of prophylactic surgery among women testing positive.
- ◆ **Alternative Imaging to Evaluate an Abnormal Mammogram:** Women were very satisfied with the alternative tests, and sestamibi was rated as the most comfortable of the tests, compared to routine mammography. Some women were concerned about the inconvenience of traveling to a tertiary care facility to undergo testing. The majority of women would be willing to spend a substantial sum of money to avoid a biopsy, but only if the tests had the same accuracy as biopsy. When the accuracy decreases to 95%, fewer women would be willing to pay to avoid biopsy.
- ◆ **Clinical Relevance of Serendipitous MRI Lesions:** Lesions noted on breast MRI taken for the evaluation of a different lesion have an extremely low probability of being cancer if the primary lesion is not malignant.
- ◆ **Non-Clinical Outcomes of Phase 1 Trials to Evaluate Anti-angiogenic Agents:** The combination of TNP-470 plus paclitaxel did not significantly impact on health-related quality of life in the Phase I trial, although participants baseline health was reasonably low.
- ◆ **14 Publications**
- ◆ **13 Newly funded grants**

4.0 REPORTABLE OUTCOMES

4.1 Manuscripts

Mandelblatt JS, Yabroff KR. Effectiveness of interventions designed to increase mammography use: a meta-analysis of provider-targeted strategies. *Cancer Epidemiol Biomarkers Prev* 1999;8:759-67.

Mandelblatt JS, Yabroff KR. Interventions targeted towards patients to increase mammography use. *Cancer Epidemiol Biomarkers Prev* 1999;8:749-57.

Mandelblatt JS, Fryback DG, Weinstein MC, Russell LB, Gold MR. Assessing the effectiveness of health interventions for cost-effectiveness analysis. *J Gen Intern Med* 1997;12:551-8.

Mandelblatt JS, Gold K, O'Malley AS, Taylor K, Cagney K, Hopkins JS, Kerner J. Breast and cervix cancer screening among multiethnic women: role of age, health, and source of care. *Prev Med* 1999;28:418-25.

Mandelblatt JS, Yabroff KR, Kerner J. Equitable access to cancer services: a review of barriers to quality care. *Cancer* 1999;86:2378-90.

Mandelblatt JS, Hadley J, Kerner JF, et al. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physician influences. *Cancer* 2000;89:561-3.

Lawrence WF, Smith SS, Baker TB, Fiore MC. Does over-the-counter nicotine replacement therapy improve smoker's life expectancy? *Tobacco Control* 1998;7:364-368.

Lawrence WF, Liang W, Mandelblatt JS, Gold KF, Freedman M, Ascher SM, Trock BJ, Chang P. Serendipity in diagnostic imaging: magnetic resonance imaging of the breast. *J Natl Cancer Inst* 1998; 90:1792-800.

Lawrence WF, Peshkin BN, Liang W, Isaacs C, Lerman C, Mandelblatt JS. Cost of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations. *Cancer Epidemiol Bio Prev*. Accepted with revisions, 2001.

Lawrence WF, Liang W, Isaacs C, Lerman C, Peshkin B, Hwang Y, Yi B, Mandelblatt JS. Cost-effectiveness of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations for high-risk women. Submitted, 2001.

Lawrence WF, Liang W, Hwang Y, Peshkin B, Isaacs C, Lerman C, Mandelblatt JS. Health preferences of women at high risk for breast cancer genetic susceptibility mutations. Submitted, 2001.

Liang W, Lawrence WF, Burnett C, Hwang Y, Freedman M, Trock B, Mandelblatt JS. Acceptability of diagnostic tests for breast cancer. Submitted, 2001.

O'Malley AS, Kerner J, Johnson AE, Mandelblatt JS. Acculturation and breast cancer screening among hispanic women in New York City. *Am J Public Health* 1999;89:219-227.

O'Malley AS, Lawrence W, Liang W, Yabroff R, Lynn J, Kerner J, Mandelblatt JS. Feasibility of mobile cancer screening and prevention. Submitted, 2001.

4.2 Funded Grants:

Mandelblatt J, Lawrence W, Hwang YT. Breast Cancer: Preparing for Survivorship, National Cancer Institute (PI: P. Ganz)(1996-2001).

Schwartz M, Lawrence WF. Interactive Decision-Aid for BRCA1/2 Mutation Carriers, National Cancer Institute (1999-2004).

Hughes C, Lawrence W. A Comparison of Counseling Methods for BRCA1/2 Mutation Carriers. National Cancer Institute (1998-2002).

Schwartz M, Lawrence WF. BRCA1/2 Testing in breast Cancer Patients, National Cancer Institute (1997-2002).

Ingham J, Lawrence WF, Mandelblatt JS, Taylor K, Yabroff R. Cohort Study of Cancer Patient Caregiver Outcomes, National Institute of Nursing Research (1999-2002).

Lawrence WF. Breast Cancer Genetic Susceptibility Testing: A Primary Care Perspective, Department of the Army, (2000-2002).

Lawrence WF. Cost-Effectiveness of SLC6A3 Gene Testing to Direct Smoking Cessation Therapy.

National Cancer Institute, TTURC (PI: C Lerman)

Mandelblatt JS, Lawrence WF, Taylor K. Decisions and Outcomes of Chemotherapy in the Elderly, National Institute on Aging (2001-2005).

Taylor, K. Prostate Cancer Screening in the PLCO Trial: Quality of Life and Adherence (Ancillary study to the PLCO Cancer Screening Trial), National Cancer Institute (1997-1998).

Mandelblatt J, Lawrence W, Liang W, Yabroff R. Towards the Optimal Screening Strategies in the Elderly, National Cancer Institute (2000-01).

Mandelblatt J, Lawrence W, Liang W, Yabroff R. Cost Effectiveness of Breast Cancer Screening Across the Spectrum of Care, National Cancer Institute (2000-04).

Stearns V, Lawrence W. Tamoxifen Genetics. National Institute of General Medical Sciences (U-01 PI: D Flockhart) (2000-2005).

Burnett CB. Patient Decision Making in Phase I Cancer Trials, NINR/NCI (1998-2001).

4.3 Other:

◆ 2 Presentations at National Meetings

- Cost of Genetic Counseling and Testing for Women at High-Risk for Breast Cancer Genetic Susceptibility Mutations. Presented at the 1999 Society of General Internal Medicine Annual Meeting.

- Cost-Effectiveness of Genetic Counseling and Testing for BRCA1 and BRCA2 Breast Cancer Genetic Susceptibility Mutations for High-Risk Women. Presented at the 2000 DOD Era of Hope Meeting.

◆ Development of junior faculty (Dr. Liang)- Dr. Liang, who has been the Core coordinator, has recently submitted a revised career development award to the National Cancer Institute to study cancer outcomes in older Chinese women.

- ◆ Appointment of Dr. Mandelblatt as Vice Chair of the Clinical Economics Sub-Committee of the CALBG Cancer Control and Health Outcomes Committee
- ◆ Appointment of Dr. Lawrence as member of the Clinical Economics Sub-Committee of the CALBG Cancer Control and Health Outcomes Committee
- ◆ Promotion of Dr. Mandelblatt to Director, Cancer Control Program, Lombardi Cancer Center
- ◆ Promotion of Dr. Mandelblatt to Acting Director, Division of Health Behaviors and Outcomes, Department of Oncology, Georgetown University Medical Center
- ◆ Appointment of Dr. Mandelblatt to the National Cancer Institute expert "Cancer Outcomes Measurement Working Group"
- ◆ Development of a Quality of Life Library

5.0 CONCLUSIONS: The science of conducting outcomes research, including economic evaluations in oncology practice, is a relatively new discipline and one which is rapidly evolving. This Outcomes Core has extended the state-of-the-art science by convening a unique cross-disciplinary research team with the methodological expertise to evaluate the costs and benefits of new and existing cancer services. Incorporating clinical and economic outcomes into center-wide research focused on translating new advances from the laboratory to individuals, and from a cancer center to community-based hospitals, managed care organizations, and community groups is allowing Lombardi Cancer Center to expand its leadership position to informing ongoing clinical, policy and resource allocation debates. As we continue to balance efforts to contain costs while providing care that maximizes health and quality of life, cost-effectiveness and other outcomes analyses, such as those conducted by this Core, will be critical to understanding which treatments work best, under which circumstances, for which populations, and at what cost.

6.0 REFERENCES

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Lawrence WF, Peshkin BN, Liang W, Isaacs C, Lerman C, Mandelblatt JS. Cost of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations. *Cancer Epidemiol Bio Prev*. Accepted with revisions, in press, 2001.

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Lawrence WF, Liang W, Isaacs C, Lerman C, Peshkin B, Hwang YT, Yi B, Mandelblatt JS. Cost-effectiveness of genetic testing and counseling for BRCA1 and BRCA2 mutations in high-risk women. Submitted, 2001.

Lerman C, Hughes C, Croyle RT, et al. (2000). Prophylactic surgery decisions and surveillance practices one year following BRCA1/2 testing. *Prev Med*, 31:75-80.

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O'Leary JF, Fairclough DL, Jankowski MK, et al. (1995). Comparison of time-tradeoff utilities and rating scale values of cancer patients and their relatives: Evidence for a possible plateau relationship. *Medical Decision Making*, 15, 132-37.

Rubin HR, Gandek B, Rogers WH, Kosinski M, McHorney CA, Ware JE. Patients' ratings of outpatient visits in different practice settings. *JAMA*. 1993; 270:835-840.

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KEY ACCOMPLISHMENTS SUMMARY

KEY ACCOMPLISHMENTS

Project 1

Impact of Genetic Testing for Breast Cancer Susceptibility

- Uptake: The high rates of uptake of both genetic counseling and testing in our study are higher than most published estimates. It is likely that the fact that these services were offered at no cost was an incentive to participation as commercial costs for testing may be as much as \$2,580. In addition, participants were very concerned about the possibility of genetic discrimination; however, this research program offered several provisions to protect confidentiality.
- Predictors of uptake: These data are the first to document predictors of uptake in a high-risk clinically based population. For example, among breast cancer survivors, those who perceived their risk for ovarian cancer to be high were most likely to be tested, while those with high levels of spiritual faith were less likely to get tested. In addition to the importance of investigating these findings in future studies, these are issues that may be raised in the context of genetic counseling. (Schwartz et al., 2000)
- Baseline screening for breast and ovarian cancer: Breast and ovarian screening uptake in healthy women from hereditary breast cancer families is suboptimal, even for women over age 50, for whom annual mammography is clearly indicated. Having at least 1 relative with ovarian cancer was very strongly associated with ovarian cancer screening. Perceived and objective cancer risks were also independent predictors of uptake for CA-125 and ultrasound. No association between cancer worries/distress and either breast or ovarian cancer screening was found. Health care providers and patients need to be better informed about screening recommendations for high risk women, and the fact that women with a strong family history of breast cancer may also be at-risk for ovarian cancer. Follow-up of women will determine if genetic counseling/testing had an impact on screening behaviors. (Isaacs et al., in preparation)
- Impact: We found no evidence for adverse effects on perceived risk, cancer-related distress, or global distress in our cohort of high-risk women (i.e., affected probands and unaffected relatives) followed for six months post-counseling. Psychological benefits, reflected in decreases in cancer-related distress, were observed among unaffected relatives. This study is the first large clinic-based prospective analysis confirming the absence of psychological sequelae of BRCA1/2 testing in most participants. We did, however, observe modestly elevated distress levels in those who received positive or uninformative results. Therefore, these individuals may benefit from continued support. (Schwartz et al., manuscript in preparation for JNCI). In addition, we found that prior to BRCA1/2 test result disclosure, women's levels of psychological distress varied depending upon their coping style, although this was not true immediately after results were disclosed. At that time, carriers experienced significantly more distress than noncarriers, and effect which was not modified by coping style. This information suggests certain assessments and interventions based on individual coping style may need to be utilized or developed for use prior to and following the receipt of test results. (Tercyak et al., Health Psychology, in press)
- Cost: The costs for genetic counseling are low relative to the costs involved in BRCA1/2 testing. Thus, findings derived from cost analyses in this research setting suggest that, in clinical practice, replacement of comprehensive genetic counselor counseling with a shorter time of physician counseling would not significantly lower overall costs.

Project 2***A Coordinated Approach to Breast Cancer Diagnosis***

- This Core was successful in recruiting patients and gathering data on patients with both benign and malignant disease.
- The results of the correlation of Sestamibi with mammographic categories are being analyzed and are being prepared for presentation.
- We have added high-resolution ultrasound and Doppler measurements to our protocol and have explored as a pilot project its substitution for MRI for the detection of second breast primary tumors and measurements of disease extent. We have changed several aspects of the protocol based on new knowledge.
- The project provided opportunities for the correlated analysis of several potentially highly promising new methods for breast imaging including digital mammography, sono-elastography, high resolution gamma camera and electrical impedance imaging of the breast. Each of these new technologies has shown improvement over the time of the project.
- Based on the affiliation with Howard University, we have instituted a new Partnership Grant to help train their Electrical Engineering graduate students in aspects of breast disease and imaging (P20 grant awarded).
- While we have not succeeded in the primary goal of finding methods to avoid breast biopsies that show only benign disease, the project has resulted in several advances in new imaging methods for breast cancer and in the training of Computer Science and Biomedical Engineering students who can continue to advance the field.
- We have been able to assist several small companies in their development of new promising technologies utilizing nuclear breast imaging, nuclear imaging guided breast biopsies, electrical impedance imaging and spectroscopy, and in the development towards a new transmission ultrasound system for breast imaging and image guided biopsy.
- This project has resulted in additional successful grants in experimental ultrasound development and testing, electrical impedance imaging and spectroscopy, and in a Partnership grant for training Computer Science and Electrical Engineering Students in aspects of imaging breast disease.

Project 3***Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer***

- Completed Phase I study of TNP-470 plus paclitaxel
- Completed Phase II study of thalidomide

Core 1

Patient Accession Core

- Based on an analysis of this experience, and a review of other successful and unsuccessful efforts at minority clinical trials accrual, the LCC proposed to expand minority accrual to breast cancer research trials by expanding an existing network of oncology office practices, and their affiliated internist, ob/gyn and surgical practices. Focus was directed on recruiting office practices that had a large minority patient population. LCC attempted to build on-going relationships where patients could be treated on protocols locally, and the trust and understanding engendered among community physicians and patients by the LEARN program could improve referral to Georgetown protocols where such referrals are necessary. Unfortunately, our efforts were less than successful. Therefore, in August 2000, we requested and obtained approval to reallocate these funds to provide web-based infrastructure for clinical trials information.

Core 2

Cancer Clinical and Economics Core

- ◆ **Utilities:** In our examination of the utilities, or preferences, of women for the downstream consequences of testing and counseling for BRCA1/2, we found several interesting results. First, among women with high risk for a mutation, cancer patients rated cancer health states higher than the non-cancer patients did. Also, there were no significant differences between women's ratings of lumpectomy, mastectomy, and bilateral prophylactic mastectomy for early breast cancer. Based on these findings we conclude that women re-adjust expectations after a cancer diagnosis, and that treatment choices are equivalent, and should be made based on shared-decision making that considers an individual woman's preference.
- ◆ **Costs of BRCA1/2 Counseling and Testing:** The costs for genetic counseling are low relative to the costs involved in BRCA1/2 testing. Thus, findings derived from cost analyses in this research setting suggest that, in clinical practice, replacement of comprehensive genetic counselor counseling with a shorter time of physician counseling would not significantly lower overall costs.
- ◆ **Cost-Effectiveness of BRCA1/2 Counseling and Testing:** Screening women with a high prior probability of having a mutation is cost-effective by current standards; screening low risk women is fairly costly per year of life saved. The ultimate cost and benefits of testing in general practice will depend on mutation probability and the rate of use of prophylactic surgery among women testing positive.
- ◆ **Alternative Imaging to Evaluate an Abnormal Mammogram:** Women were very satisfied with the alternative tests, and sestamibi was rated as the most comfortable of the tests, compared to routine mammography. Some women were concerned about the inconvenience of traveling to a tertiary care facility to undergo testing. The majority of women would be willing to spend a substantial sum of money to avoid a biopsy, but only if the tests had the same accuracy as biopsy. When the accuracy decreases to 95%, fewer women would be willing to pay to avoid biopsy.
- ◆ **Clinical Relevance of Serendipitous MRI Lesions:** Lesions noted on breast MRI taken for the evaluation of a different lesion have an extremely low probability of being cancer if the primary lesion is not malignant.

- ◆ **Non-Clinical Outcomes of Phase 1 Trials to Evaluate Anti-angiogenic Agents:** The combination of TNP-470 plus paclitaxel did not significantly impact on health-related quality of life in the Phase I trial, although participants baseline health was reasonably low.
- ◆ **14 Publications**
- ◆ **13 Newly funded grants**

REPORTABLE OUTCOMES SUMMARY

Project 1

Impact of Genetic Testing for Breast Cancer Susceptibility

- Peer-reviewed publications/commentaries

Brunet JS, Ghadirian P, Rebbeck TR, Lerman C, Garber JE, Tonin PN, Abrahamson J, Foulkes WD, Daly M, Wagner-Costalas J, Godwin A, Olopade OI, Moslehi R, Liede A, Futreal PA, Weber BL, Lenoir GM, Lynch HT, Narod SA. Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. Journal of the National Cancer Institute 1998; 90(10):761-766.

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Gilewski T, Norton L, Brown K, Schulz C, Hampel H, Schluger A, Giulotto E, Zoli W, Ravaioli A, Nevanlinna H, Pyrhonen S, Rowley P, Loader S, Osborne MP, Daly M, Tepler I, Weinstein PL, Scalia JL, Michaelson R, Scott RJ, Radice P, Pierotti MA, Garber JE, Isaacs C, Peshkin B, Lippman ME, Dosik MH, Caligo MA, Greenstein RM, Pilarski R, Weber B, Burgemeister R, Frank TS, Skolnick MH, Thomas A. BRCA1 sequence analysis in women at high risk for susceptibility mutations: risk factor analysis and implications for genetic testing. Journal of the American Medical Association 1997; 278:1242-1250.

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- **Manuscripts under review or in progress**

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DeMarco TA, Peshkin BN, Brogan BM. Genetic counseling for breast and ovarian cancer susceptibility: closing the gap. Manuscript being revised for submission to the Journal of Genetic Counseling.

Isaacs C, Peshkin BN, Schwartz M, DeMarco TA, Main D, Lerman C. Breast and ovarian cancer screening practices in healthy women with a strong family history of breast or ovarian cancer. Manuscript in preparation.

Lawrence WF, Peshkin BN, Liang W, Isaacs C, Lerman C, Mandelblatt JS. Cost of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations. Cancer Epidemiology Biomarkers and Prevention, (under revision).

Peshkin BN, DeMarco TA, Brogan BM, Lerman C, Isaacs C. BRCA1/2 testing: complex themes in result interpretation. Revised manuscript under review at Journal of Clinical Oncology.

Schwartz MD, et al (authorship to be determined). The impact of BRCA1/BRCA2 mutation testing on psychological distress in a clinic-based sample. Manuscript in preparation for Journal of the National Cancer Institute.

- **Abstracts**

Chittenden A, Wonderlick A, Peshkin B, Patenaude A, Garber J. BRCA1 testing in a transsexual male. Journal of Genetic Counseling 1999; 8:379 (abstract).

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Ganguly T, Citron M, Stott J, Isaacs C, Peshkin B, Godmilow L, Weber B, Ganguly A. Novel BRCA mutations in African American individuals with breast and ovarian cancer. American Journal of Human Genetics 1998; 63(4)Supp:366 (abstract).

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Isaacs C, Peshkin B, Reutenauer J, Reed M, Main D, Lerman C. Cancer screening practices in women from high risk breast cancer families. Proceedings of the American Society of Clinical Oncology 1997; 17:1916 (abstract).

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Weber BL, Punzalan C, Eisen A, Lynch HT, Narod SA, Garber JE, Isaacs C, Daly MB, Neuhausen SL, Rebbeck TR. Ovarian cancer risk reduction after bilateral prophylactic oophorectomy (BPO) in BRCA1 and BRCA2 mutation carriers. American Journal of Human Genetics 2000; 67(2)Supp:251 (abstract).

- **Book chapters**

Benkendorf JL, Peshkin BN, Lerman C. Impact of genetic information and genetic counseling on public health. In: Khoury MJ, Burke W, Thomson EJ, eds. Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease. New York: Oxford University Press, 2000: pages 361-383.

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Lerman C, Peshkin BN. Psychosocial issues in BRCA1/2 testing. In: Bowcock AM (ed.), Breast Cancer: Molecular Genetics, Pathogenesis, and Therapeutics (Contemporary Cancer Research series). NJ: Humana Press, 1999: pages 247-266.

- **Other Reportable Outcomes**

Registry development. Participants in the CARE program are invited to contribute to our Familial Cancer Registry. This registry is a repository for blood and tumor DNA, as well as pathology information. A database containing risk factor information has also been developed. Data from CARE participants, combined with data from several other sites, has been used to determine the effects of oral contraceptives,

cigarette smoking, parity, tamoxifen, prophylactic surgery, and other factors on cancer risks in mutation carriers (see publication list).

Funding applied for based on this work. Based in part from preliminary data on this work and the "standard genetic counseling" protocols refined through this grant, funding for additional studies has been awarded. For example, Chanita Hughes, PhD is the Principal Investigator for a new DOD funded study, "Genetic Counseling for Breast Cancer Susceptibility in African American Women." This is a randomized study of a culturally tailored genetic counseling protocol, modified from the one used for the current study. Dr. Hughes is also the PI for an NIH supported study, "Comparing Models of Counseling for BRCA1/2 Testing." This randomized study is evaluating the impact of psychosocial telephone counseling versus standard genetic counseling in female mutation carriers. Once that study completes accrual, Marc Schwartz, PhD will begin recruitment for his study funded by NIH, "Interactive Decision-Aid for BRCA1/2 Mutation Carriers." This is also a randomized study evaluating the impact of a CD-ROM-based intervention versus standard genetic counseling on decisions about breast cancer screening and prevention, and quality of life in female mutation carriers.

High-risk individuals ascertained through the CARE program may also be invited into the NIH funded "Cancer Genetics Network." This is a grant to develop an infrastructure of nationwide resources that will enable researchers to have access to interested participants for cancer genetics studies. In addition, a subcontract was recently awarded by NIH to study the efficacy of prophylactic mastectomy and oophorectomy in mutation carriers, for which Claudine Isaacs, MD is the principal investigator.

Training supported by this award. Since 1998, six genetic counseling students from three accredited master's level training programs (National Human Genome Research Institute, University of Michigan, and Howard University) completed clinical rotations at Georgetown University. Under the close supervision of the genetic counselors, these individuals had an opportunity to observe and take part in the genetic counseling of research participants.

Project 2

A Coordinated Approach to Breast Cancer Diagnosis

Presentations/Papers

- Presentation of data at the 1998 annual meeting of the American Association for Cancer Research (Haddad, et al): This presentation of the results for culturing breast epithelial cells derived from nipple aspirate fluid, and performing comparative genomic hybridization (CGH) on the DNA obtained from the expanded cell number was (to our knowledge) the first report of anyone culturing cells from nipple aspirate fluid. It was definitely the first report of performing on these cells.
- Lawrence WF, Liang W, Mandelblatt JS, Gold KF, Freedman M, Ascher SM, Trock BJ, Chang P. Serendipity in diagnostic imaging: magnetic resonance imaging of the breast. J Natl Cancer Inst 1998; 90:1792-800.

Awarded/Pending Grant Awards

- Agency: US Army Breast Cancer Program PI: Matthew Freedman, MD
Title: Electrical Impedance Imaging of the Breast: Correlation with MRI, Sestamibi and Histology with Measures of Cell Proliferation and Vascular Density.
- Foundation: Friends...you can count on PI: Matthew Freedman, MD
Title: Electrical Impedance Imaging: Explorations

- Agency: DOD Breast Cancer Research PI: Mohammed E. Chouikha, (Howard University)
Title: A Partnership Training Program in Breast Cancer Diagnosis – Concept Development of the Next Generation Breast Imaging using Digital Library Techniques and Networks
- Pending Award from DOD Diagnostic and Surgical Breast Imaging Program
PI: Matthew Freedman, MD
Title: High-Resolution Speckle-Free Ultrasound Imaging System – A Potential solution for Detecting Missed Breast Cancer

Project 3

Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer

1. Baidas S, Bhagava P, Isaacs C, Rizvi N, Trocky N, Pipkin T, Hayes DF, Chen H, Marshall J. A phase I study of the combination of TNP470 and paclitaxel in patients with advanced cancer. Proc. Am. Soc. Clin. Oncol. 19:205a, 2000.
2. Baidas S, Isaacs C, Crawford J, Winer E, Fleming G, Harris L, Pluda J, Hawkins M, Lippman L, Hayes DF. A phase II evaluation of thalidomide in patients with metastatic breast cancer. Proc. Am. Soc. Clin. Oncol. 18:125a, 1999.
3. Baidas S, Winer E, Fleming G, Harris L, Pluda J, Crawford J, Isaacs C, Hanfelt J, Flockhart D, Johnson M, Yamauchi H, Hawkins M, Lippman M, Hayes DF. A phase II evaluation of thalidomide in patients with metastatic breast cancer. J. Clin. Oncol. 14:2710-2717, 2000.

Core 1

Patient Accession Core

NONE TO REPORT

Core 2

Cancer Clinical and Economics Core

Manuscripts

Mandelblatt JS, Yabroff KR. Effectiveness of interventions designed to increase mammography use: a meta-analysis of provider-targeted strategies. Cancer Epidemiol Biomarkers Prev 1999;8:759-67.

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Mandelblatt JS, Gold K, O'Malley AS, Taylor K, Cagney K, Hopkins JS, Kerner J. Breast and cervix cancer screening among multiethnic women: role of age, health, and source of care. Prev Med 1999;28:418-25.

Mandelblatt JS, Yabroff KR, Kerner J. Equitable access to cancer services: a review of barriers to quality care. Cancer 1999;86:2378-90.

Mandelblatt JS, Hadley J, Kerner JF, et al. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physician influences. *Cancer* 2000;89:561-3.

Lawrence WF, Smith SS, Baker TB, Fiore MC. Does over-the-counter nicotine replacement therapy improve smoker's life expectancy? *Tobacco Control* 1998;7:364-368.

Lawrence WF, Liang W, Mandelblatt JS, Gold KF, Freedman M, Ascher SM, Trock BJ, Chang P. Serendipity in diagnostic imaging: magnetic resonance imaging of the breast. *J Natl Cancer Inst* 1998; 90:1792-800.

Lawrence WF, Peshkin BN, Liang W, Isaacs C, Lerman C, Mandelblatt JS. Cost of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations. *Cancer Epidemiol Bio Prev*. Accepted with revisions, 2001.

Lawrence WF, Liang W, Isaacs C, Lerman C, Peshkin B, Hwang Y, Yi B, Mandelblatt JS. Cost-effectiveness of genetic counseling and testing for BRCA1 and BRCA2 breast cancer susceptibility mutations for high-risk women. Submitted, 2001.

Lawrence WF, Liang W, Hwang Y, Peshkin B, Isaacs C, Lerman C, Mandelblatt JS. Health preferences of women at high risk for breast cancer genetic susceptibility mutations. Submitted, 2001.

Liang W, Lawrence WF, Burnett C, Hwang Y, Freedman M, Trock B, Mandelblatt JS. Acceptability of diagnostic tests for breast cancer. Submitted, 2001.

O'Malley AS, Kerner J, Johnson AE, Mandelblatt JS. Acculturation and breast cancer screening among hispanic women in New York City. *Am J Public Health* 1999;89:219-227.

O'Malley AS, Lawrence W, Liang W, Yabroff R, Lynn J, Kerner J, Mandelblatt JS. Feasibility of mobile cancer screening and prevention. Submitted, 2001.

Funded Grants:

Mandelblatt J, Lawrence W, Hwang YT. Breast Cancer: Preparing for Survivorship, National Cancer Institute (PI: P. Ganz)(1996-2001).

Schwartz M, Lawrence WF. Interactive Decision-Aid for BRCA1/2 Mutation Carriers, National Cancer Institute (1999-2004).

Hughes C, Lawrence W. A Comparison of Counseling Methods for BRCA1/2 Mutation Carriers. National Cancer Institute (1998-2002).

Schwartz M, Lawrence WF. BRCA1/2 Testing in breast Cancer Patients, National Cancer Institute (1997-2002).

Ingham J, Lawrence WF, Mandelblatt JS, Taylor K, Yabroff R. Cohort Study of Cancer Patient Caregiver Outcomes, National Institute of Nursing Research (1999-2002).

Lawrence WF. Breast Cancer Genetic Susceptibility Testing: A Primary Care Perspective, Department of the Army, (2000-2002).

Lawrence WF. Cost-Effectiveness of SLC6A3 Gene Testing to Direct Smoking Cessation Therapy. National Cancer Institute, TTURC (PI: C Lerman)

Mandelblatt JS, Lawrence WF, Taylor K. Decisions and Outcomes of Chemotherapy in the Elderly, National Institute on Aging (2001-2005).

Taylor, K. Prostate Cancer Screening in the PLCO Trial: Quality of Life and Adherence (Ancillary study to the PLCO Cancer Screening Trial), National Cancer Institute (1997-1998).

Mandelblatt J, Lawrence W, Liang W, Yabroff R. Towards the Optimal Screening Strategies in the Elderly, National Cancer Institute (2000-01).

Mandelblatt J, Lawrence W, Liang W, Yabroff R. Cost Effectiveness of Breast Cancer Screening Across the Spectrum of Care, National Cancer Institute (2000-04).

Stearns V, Lawrence W. Tamoxifen Genetics. National Institute of General Medical Sciences (U-01 PI: D Flockhart) (2000-2005).

Burnett CB. Patient Decision Making in Phase I Cancer Trials, NINR/NCI (1998-2001).

Other:

- 2 Presentations at National Meetings:

Cost of Genetic Counseling and Testing for Women at High-Risk for Breast Cancer Genetic Susceptibility Mutations. Presented at the 1999 Society of General Internal Medicine Annual Meeting.

Cost-Effectiveness of Genetic Counseling and Testing for BRCA1 and BRCA2 Breast Cancer Genetic Susceptibility Mutations for High-Risk Women. Presented at the 2000 DOD Era of Hope Meeting.

- Development of junior faculty (Dr. Liang)- Dr. Liang, who has been the Core coordinator, has recently submitted a revised career development award to the National Cancer Institute to study cancer outcomes in older Chinese women.
- Appointment of Dr. Mandelblatt as Vice Chair of the Clinical Economics Sub-Committee of the CALBG Cancer Control and Health Outcomes Committee
- Appointment of Dr. Lawrence as member of the Clinical Economics Sub-Committee of the CALBG Cancer Control and Health Outcomes Committee
- Promotion of Dr. Mandelblatt to Director, Cancer Control Program, Lombardi Cancer Center
- Promotion of Dr. Mandelblatt to Acting Director, Division of Health Behaviors and Outcomes, Department of Oncology, Georgetown University Medical Center
- Appointment of Dr. Mandelblatt to the National Cancer Institute expert "Cancer Outcomes Measurement Working Group"
- Development of a Quality of Life Library

PERSONNEL RECEIVING SALARY SUPPORT ON DAMD17-96-C-6069 DURING THE GRANT PERIOD

PROJECT 1: OUTCOMES OF GENETIC TESTING	PROJECT 2: DETECTION AND DIAGNOSIS	PROJECT 3: PHASE I, II, AND III CLINICAL TRIALS
Caryn Lerman, PhD	Matthew Freedman, MD	Daniel Hayes, MD
Bruce Trock, PhD	Bruce Trock, PhD	John Marshall, MD
Claudine Isaacs, MD	Bassem Haddad, MD	Said Baidas, MD
Jeanne Mandelblatt, MD	Anita Sarcone	Claudine Isaacs, MD
Tiffani DeMarco, MS	Michelle Brotzman	Nina Trocky, RN
Audra Doss, MS	Jennifer Hu, PhD	Rebecca Slack
David Main, MA, MS	Polly Nesbit	Ruth Foelber, RN
Annalisa Dialino, BA	S. Ray	Michael Hawkins, MD
Lisa Smith, BA		John Hanfelt, PhD
Susan Marx		Kimberly Phipps, BSN, MSN
Jennifer Rocca		
Beth Peshkin, MS		
Andres Gomez, MPH		
ADMINISTRATIVE CORE	CORE 1: PATIENT ACCESSION	CORE 2: OUTCOMES EVALUATION
Donna Ruffin	Jon Kerner, PhD	Jeanne Mandelblatt, MD
	Tracey Thomas	Yi Ting Hwang, PhD
	Lenora Johnson, MS	Wenchi Liang, PhD
	Anna Marie Ryan, MS	William Lawrence, MD
	Randal Mickens	Julia Rowland, PhD
	Shermaine Pender	Karen Gold, PhD
		Caroline Burnett, RN

FINAL REPORT ABBREVIATIONS

ASCO	American Society of Clinical Oncology
BCRC	Breast Cancer Resource Committee
BDL	Breast Ductal Lavage
CAB	Community Advisory Board
CABCAD or CAB/CAD	Coordinated Approach to Breast Cancer Diagnosis
CARE	Cancer Assessment and Risk Evaluation
CATI	Computer Assisted Telephone Interview
CEAs	Cost-Effectiveness Analyses
CGH	Comparative Genomic Hybridization
DNA	Deoxyribonucleic Acid
DOD	Department of Defense
ELISA	Enzyme-Linked Immunosorbent Assay
EQL	Education for Quality Living
FACT-B	Name of Specific Quality of Life Instrument
FDA	Food and Drug Administration
GA	Georgia
GUMC	Georgetown University Medical Center
HMO	Health Maintenance Organization
HUI	Health Utilities Index
LCC	Lombardi Cancer Center
LEARN	Lombardi Education and Research Network
LERC	Lombardi Extramural Research Consortium
LRS	Linear Rating Scale
LYS	Life Years
MMG	Matthews Media Group
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NAF	Nipple Aspirate Fluid
NPV	Negative Predicted Value
PAC	Patient Accession Core
QALYs	Quality-Adjusted Life Years
QOL	Quality of Life
SELDI	Ionization Spectroscopy
TTO	Time-Trade-Off
WTP	Willingness to Pay

APPENDIX PACKET

PROJECT 1

Appendix 1: Article Reprints and CARE Educational Materials
Appendix 2: Selected Abstracts

PROJECT 3

Appendix 1: Baidas Reprint

CORE 2

Appendix 1: Outcomes Core Related Publications
Appendix 2: Quality of Life Library
References and Sample Instrument Abstraction Forms

PROJECT 1: APPENDIX 1
ARTICLE REPRINTS AND CARE EDUCATIONAL MATERIALS

JOURNAL OF HEALTH CARE LAW & POLICY

Symposium: "Testing and Telling?: Implications for Genetic Privacy, Family Disclosure and the Law"

ARTICLES

Biological Truths and Legal Fictions

R. Alta Charo, JD

Medical Implications of the Genetic Revolution

*Monique K. Mansoura, PhD
Francis S. Collins, PhD*

Family Disclosure in Genetic Testing for Cancer Susceptibility:
Determinants and Consequences

*Caryn Lerman, PhD
Beth N. Peshkin, MS
Chanita Hughes, PhD
Claudine Isaacs, MD*

What Should the Law Say About Disclosure of Genetic
Information to Relatives?

Ellen Wright Clayton, MD, JD

Ethical Responsibilities of Patients and Clinical Geneticists

Allen Buchanan, PhD

NOTES

Boling v. Romer: Federal Courts Condone Forced Withdrawal
of Blood for DNA Data Banks Despite
Constitutional Concerns

C. Teddy Li

The Argument Against a Physician's Duty to Warn for Genetic
Diseases: The Conflicts Created by *Safer v. Estate of Pack*

Angela Liang



University of Maryland School of Law
Law & Health Care Program

Volume 1
No. 2
1998

**FAMILY DISCLOSURE IN GENETIC TESTING FOR
CANCER SUSCEPTIBILITY:
DETERMINANTS AND CONSEQUENCES†**

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BETH N. PESHKIN M.S.,**
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† We would like to thank our study collaborators, including Drs. Henry Lynch, Stephen Lemon, Steven Narod, and Marc Schwartz. Other members of the research team contributing to family ascertainment, counseling, and evaluation include Jeri Reutenauer, M.S., Tiffani DeMarco, M.S., David Main M.A., M.S., Carol Anne Kavanagh, M.A., Margaret Reed, B.A., Kristen Willard, B.A., Rachel Manasan, B.A., Theresa Brownson, M.ed., and Susan Marx, B.S. Last, but not least, we are grateful to all of the men and women who participated in this clinical research program.

* Associate Professor in the Departments of Medicine and Psychiatry and Director of Cancer Genetics at the Lombardi Cancer Center, Georgetown University Medical Center. Dr. Lerman has participated as a member and chair of the National Human Genome Research Institute's ad hoc study section: Ethical, Legal, and Social Implications of Human Genetics Research and is a member of the National Cancer Institute's Board of Scientific Advisors. She has conducted extensive research on the psychosocial implications of genetic testing. For this work she has received an award from the American Psychological Association for Outstanding Contributions to Health Psychology.

** Certified Genetic Counselor and Research Instructor at Georgetown University. Ms. Peshkin is the Senior Genetic Counselor and Project Director for a Department of Defense funded grant at Georgetown, "Impact of Genetic Testing for Breast Cancer Susceptibility." She is also a co-investigator on other funded grants related to genetic testing. With over four years experience in cancer genetic counseling, she has counseled several hundred individuals about issues related to genetic testing. She has also contributed to the development of educational programs and materials for professionals and patients.

*** Project Director for two multi-institutional grants related to genetic testing in hereditary breast and colon cancer families at the Lombardi Cancer Center, Georgetown University Medical Center. Dr. Hughes is currently conducting research on the role of family communication in the genetic counseling process, ethnic differences in responses to genetic testing for cancer susceptibility, and the development and evaluation of culturally-sensitive genetic counseling protocols.

**** Assistant Professor of Medicine at the Georgetown University Medical Center and board certified medical oncologist with expertise in breast cancer. Dr. Isaacs is the Medical Director of the Cancer Assessment and Risk Evaluation Program. She is the co-principal investigator of a National Cancer Institute ("NCI") funded study to determine the impact of genetic counseling and testing in women who are newly diagnosed with breast cancer and is the principal investigator of an NCI funded study on educating physicians about hereditary breast cancer. She is also a co-investigator on several other NCI and Department of Defense funded breast cancer treatment or chemoprevention studies.

I. INTRODUCTION AND OVERVIEW

The isolation of the BRCA1 and BRCA2 genes has made it possible to identify women at increased risk for breast and ovarian cancer, thereby facilitating informed decisions about surveillance and cancer prevention options.¹ Despite these potential medical benefits, the identification of carriers of deleterious mutations raises numerous psychological and social challenges for those being tested and for their family members.² One of the more pressing and least studied issues involves the process and outcomes of disclosure of genetic information within families. The present article addresses family disclosure of information about genetic testing for cancer susceptibility. Following an overview of the clinical aspects of family disclosure and the empirical literature on this topic, we present our preliminary data on the determinants and outcomes of disclosure of BRCA1 and BRCA2 ("BRCA1/2") genetic information within hereditary breast cancer families. These data are supplemented with case studies of patients, highlighting the motivations for and against disclosure and il-

1. See Douglas F. Easton et al., *Breast and Ovarian Cancer Incidence in BRCA1-Mutation Carriers*, 56 AM. J. HUM. GENETICS 265 (1995); Deborah Ford et al., *Risks of Cancer in BRCA1-Mutation Carriers*, 343 LANCET 692 (1994); Richard Wooster et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2*, 378 NATURE 789, 790 (1995). These studies, the first two of which are from the Breast Cancer Linkage Consortium, established that the lifetime risks of breast and ovarian cancer associated with BRCA1 mutations are about 85% and 63%, respectively, with onset often at a younger age than observed in the general population. See Easton et al., *supra*, at 270; Ford et al., at 270. Risks for breast cancer in women with BRCA2 mutations were found to be comparable to BRCA1, but the ovarian cancer risks were lower. See Wooster, *supra*, at 790. Prostate cancer risks appear to be elevated in male BRCA1 carriers. In addition, colon cancer risks may be elevated in men and women with a BRCA1 or BRCA2 mutation, and other more rare cancers have been associated with BRCA2 alterations. See *id.* Another study found lower risks of breast and ovarian cancer associated with three common mutations in Ashkenazi Jewish individuals who did not necessarily have a family history of cancer. Jeffery P. Struwing et al., *The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 Among Ashkenazi Jews*, 336 NEW ENG. J. MED. 1401, 1401 (1997). The risks were still markedly elevated over the general population. See *id.* In addition, prostate cancer risks were elevated, though colon cancer risks were not. See *id.*; see also generally Wylie Burke et al., *Recommendations for Follow-up Care of Individuals with an Inherited Predisposition to Cancer: II. BRCA1 and BRCA2*, 277 JAMA 997 (1997) (discussing provisional recommendations for early detection and cancer prevention in individuals with a BRCA1 or BRCA2 mutation, including heightened surveillance often commencing at an early age, and reviewing the data regarding the options for prophylactic surgery).

2. See Caryn Lerman et al., *BRCA1 Testing in Families with Hereditary Breast-Ovarian Cancer: A Prospective Study of Patient Decision Making and Outcomes*, 275 JAMA 1885, 1889 (1996) (discussing patients' perception of the benefits, limitations, and risks of testing, which included social concerns such as fears about insurance discrimination, and concerns about emotional adaptation and response of relatives to test results).

lustrating key counseling issues. Finally, we summarize these data and discuss the health-related and legal implications.

II. FAMILY DISCLOSURE OF GENETIC INFORMATION IN THE BRCA1 AND BRCA2 GENETIC COUNSELING SETTING

Disclosure of genetic information about cancer susceptibility has numerous implications for patients, family members, health care providers, and researchers. In the clinical and research settings, disclosure of one's mutation status provides a gateway for other family members to have access to genetic testing research protocols. Typically, BRCA1/2 testing within a family begins with a woman who has been diagnosed with breast or ovarian cancer, often at a young age (referred to as the proband). If a known disease-conferring mutation is identified, other first-degree relatives such as siblings and children have a 50% likelihood of also carrying the mutation and having an increased cancer risk.³ In some families, it is also possible to identify more distant relatives who are at increased risk such as nieces, nephews, and cousins. With knowledge of the particular mutation carried by the proband, it becomes possible to offer testing to other family members for that same mutation.⁴ However, in the interest of protecting the confidentiality of the participant, researchers or clinicians should not approach other family members about their risk status or about testing. A common process, employed in most clinical research settings, is to discuss with the proband the implications of her test result for other family members as well as the attendant personal and social risks.⁵ Probands are then given the option to contact their relatives directly, to have the health care provider contact their relatives,

3. See generally Barbara B. Biesecker et al., *Genetic Counseling for Families with Inherited Susceptibility to Breast and Ovarian Cancer*, 269 JAMA 1970 (1993). BRCA1 and BRCA2 alterations are inherited in an autosomal dominant fashion, which means that each child of a parent with an alteration has a 50% chance of having the same alteration. See generally *id.* Male and female offspring are at equal risk of inheriting BRCA1 and BRCA2 mutations. See generally *id.*

4. Within high-risk families, the advantage to first testing a woman with breast or ovarian cancer diagnosed at an early age is that she is most likely to carry an alteration if one is present within the family. See Maggie Ponder & Josephine M. Green, *BRCA1 Testing: Some Issues in Moving from Research to Service*, 5 PSYCHO-ONCOLOGY 223, 223 (1996). It is possible to test individuals without knowledge of whether there is a BRCA1 or BRCA2 mutation present in their family (e.g., if all relatives with breast or ovarian cancer are deceased). *Id.* at 228. In such scenarios, a positive result will still yield useful information. However, a negative test result is not considered to be informative because it is not possible to distinguish whether the patient did not inherit a mutation present in her family or whether there is no detectable BRCA1 or BRCA2 mutation in the family. *Id.* at 227.

5. See Biesecker et al., *supra* note 3, at 1972-73. The authors concluded that a protocol to test for presymptomatic BRCA1 gene mutations should include:

or not to have any further contact with relatives.⁶ Probands are also provided with written materials to share with their relatives to facilitate the discussion.

The genetic counselor is perhaps best situated to facilitate informed decisions about family disclosure by reviewing the potential benefits and risks with the patient. In deciding whether to disclose a positive test result, one may consider the potential medical benefits for other relatives. For example, disclosure of one's own test result may be required to provide a relative with the opportunity to be tested for the specific mutation in the family, should she or he decide to do so.⁷ As mentioned above, such information may have medical value, particularly to female family members who may have a significantly elevated breast and ovarian cancer risk.⁸ A potential benefit to the proband is that disclosure of a positive test result may also elicit both emotional support and instrumental assistance in seeking and obtaining information and medical care.⁹ However, disclosure of genetic test results has potential risks, including loss of privacy, employment and insurance discrimination, and stigmatization.¹⁰ Individual distress and family conflict may also be generated by disclosure of genetic information.¹¹ Despite the importance of family disclosure, there are limited empirical data available on this topic.

(1) precounseling education and assessment; (2) a multidisciplinary team with expertise in the screening and management of breast and ovarian cancer, inheritance, DNA testing, and psychosocial counseling issues of late-onset disorders; and (3) follow-up services for the management of the increased risk for cancer as well as the residual emotional reactions on behalf of family members.

Id. at 1974; see also Lerman et al., *supra* note 2, at 1886-87 (BRCA1 counseling protocol).

6. See Biesecker et al., *supra* note 3, at 1972.

7. See Ponder & Green, *supra* note 4, at 227.

8. See Easton et al., *supra* note 1, at 265; Ford et al., *supra* note 1, at 692; Wooster et al., *supra* note 1, at 789; Struewing et al., *supra* note 1, at 1401.

9. See Biesecker et al., *supra* note 3, at 1972 (noting that a majority of family members opted to share the results of BRCA1 testing with family members in an effort to receive their support).

10. See Mark A. Rothstein, *Genetic Testing: Employability, Insurability, and Health Reform*, 17 J. NAT'L CANCER INST. MONOGRAPHS 87 (1995); Paul R. Billings et al., *Discrimination as a Consequence of Genetic Testing*, 50 AM. J. HUM. GENETICS 476 (1992).

11. See Robert T. Croyle et al., *Psychological Responses to BRCA1 Mutation Testing: Preliminary Findings*, 16 HEALTH PSYCHOL. 63, 67-69 (1997) (demonstrating that female carriers with no history of cancer or prophylactic surgery had high levels of test-related distress as measured by standard psychological assessments, but that overall, levels of general distress were not increased in this group); Henry T. Lynch et al., *A Descriptive Study of BRCA1 Testing and Reactions to Disclosure of Test Results*, 79 CANCER 2219, 2223, 2225-26 (1997) (containing anecdotal, qualitative descriptions of patient responses to testing, including sadness and survivor guilt). But see Lerman et al., *supra* note 2, at 1890 (finding that a subset of the BRCA1 carriers described in the Lynch et al. paper did not exhibit increases in depression and functional impairment when evaluated using standardized quantitative measures).

The following section provides an overview of published data about the processes and outcomes of family disclosure in the genetic testing context.

III. LITERATURE REVIEW ON FAMILY COMMUNICATION REGARDING GENETIC TESTING

Initial research on family communication about genetic testing suggests that most individuals will contact family members to obtain information about their family's medical history before counseling. Researcher Josephine Green and colleagues found that 78% of women who were scheduled for a genetic counseling session for inherited breast-ovarian cancer susceptibility communicated with a family member before their appointment to obtain family history information.¹² Specifically, probands were most likely to contact female relatives (i.e., mothers or sisters) for information about their family history.¹³ Reasons for not contacting relatives who could have provided medical information about the family included not wanting to upset the relative with discussions about cancer.¹⁴ Other reasons for not contacting relatives included lost communication with relatives and large age differences between siblings.¹⁵ This study also found that 88% of respondents shared their post-counseling summary letter with at least one relative.¹⁶

Studies of family communication about other genetic disorders (e.g., cystic fibrosis) suggest that feedback provided by relatives through verbal and/or nonverbal communication may motivate or discourage individuals from undergoing genetic testing.¹⁷ A study of cystic fibrosis testing found that a person's perceptions of their siblings' reactions to abortion was a significant predictor of usage of prenatal testing for this disorder.¹⁸ Specifically, respondents who perceived that their siblings would approve of aborting an affected

12. See Josephine Green et al., *Family Communication and Genetic Counseling: The Case of Hereditary Breast and Ovarian Cancer*, 6 J. GENETIC COUNSELING 45, 51 (1997).

13. See *id.* at 51-52.

14. See *id.* at 52.

15. See *id.*

16. See *id.* at 53.

17. See Dorothy C. Wertz et al., *Attitudes Toward the Prenatal Diagnosis of Cystic Fibrosis: Factors in Decision Making Among Affected Families*, 50 AM. J. HUM. GENETICS 1077, 1083 (1992). Cystic fibrosis is a potentially lethal genetic disease which results in the production of abnormally thick mucus which can clog the lungs and cause severe infections. See generally Francis S. Collins, *Cystic Fibrosis: Molecular Biology and Therapeutic Implications*, 256 SCIENCE 774 (1992). Carriers of the disease have no symptoms, but carrier parents have a 25% chance of having an affected child. See *id.*

18. See Wertz et al., *supra* note 17, at 1082-83.

fetus were three times more likely to use prenatal diagnosis.¹⁹ In the BRCA1/2 testing context, probands who had strong positive beliefs about the benefits of genetic testing were likely to also encourage other family members to participate in genetic testing.²⁰ These studies underscore the influence of family disclosure and communication on decision making about genetic testing.

Although most individuals may disclose their genetic test results to family members, many are reluctant to provide clinicians and researchers with direct access to these family members. In a survey of attitudes about BRCA1/2 testing among high-risk women, a majority (>80%) felt that health care providers should not disclose their test results to immediate family members without their written consent.²¹ In a cystic fibrosis screening program, only 54% of probands provided the research team with contact information for their at-risk relatives.²² Thus, most genetic testing participants desire to maintain control over the diffusion of genetic information to relatives. Further, these decisions are typically made without consulting with family members.

Willingness to communicate with family members about genetic testing and genetic disorders may be influenced by factors such as gender²³ and cultural background.²⁴ For example, women appear to be more likely to discuss genetic testing with their female relatives (i.e., daughters) than with male relatives (i.e., brothers).²⁵ This may be attributable to perceptions that only mothers, sisters, and daughters are at-risk for cancer.²⁶ Our own data on BRCA1/2 testing, presented in the next section, provide further support for gender differences in family communication about BRCA1/2 testing.

19. See *id.* at 1081-82.

20. See Andrea Farkas Patenaude et al., *Acceptance of Invitations for p53 and BRCA1 Predisposition Testing: Factors Influencing Potential Utilization of Cancer Genetic Testing*, 5 *PSYCHO-ONCOLOGY* 241, 245 (1996).

21. See Judith L. Benkendorf et al., *Patients' Attitudes About Autonomy and Confidentiality in Genetic Testing for Breast-Ovarian Cancer Susceptibility*, 73 *AM. J. MED. GENETICS* 296, 298 (1997).

22. See J.R. Sorenson et al., *Proband and Parent Assistance in Identifying Relatives for Cystic Fibrosis Carrier Testing*, 63 *AM. J. MED. GENETICS* 419, 421 (1996).

23. See Martin Richards, *Families, Kinship, and Genetics*, in *THE TROUBLED HELIX: SOCIAL AND PSYCHOLOGICAL IMPLICATIONS OF THE NEW HUMAN GENETICS* 249, 251 (Theresa Marteau & Martin Richards eds., 1996).

24. See James C. McCroskey & Virginia P. Richmond, *Willingness to Communicate: A Cognitive View*, in *COMMUNICATION, COGNITION, AND ANXIETY* 19, 31-32 (Melanie Booth-Butterfield ed., 1990).

25. See Ponder & Green, *supra* note 4, at 229-30.

26. See *id.* at 230.

Family communication may also differ among individuals with different ethnic or cultural backgrounds.²⁷ Culture has been described as a system that influences behavior and perceptions.²⁸ For example, the culture of many African Americans may generally be characterized as emphasizing the principle of spirituality and valuing interconnectedness, uniqueness, positivity, and sharing.²⁹ The culture of many European Americans is generally based on individualism and values the right to choose, honesty, sharing, and communication.³⁰ Research has shown that patterns of family communication about BRCA1 testing differ between African American and Caucasian women.³¹ In a recent study, Caucasian women at increased risk for breast cancer were significantly more likely than African American women to communicate about genetic testing with a spouse and a parent.³² Specifically, 66% of Caucasian women discussed genetic testing for hereditary breast cancer with their spouse, and 40% discussed it with a parent versus about 27% of African American women who discussed this issue with a spouse or parent.³³

IV. PRELIMINARY DATA ON THE DETERMINANTS AND OUTCOMES OF FAMILY COMMUNICATION ABOUT BRCA1 AND BRCA2 TESTING

A. *Research Questions*

The published literature described previously provides some initial insights into the processes and determinants of communication of genetic information within families. However, it is important to assess communication processes and outcomes in a systematic manner and to address several key questions about family communication which are unanswered at present. Our research on BRCA1/2 testing in hereditary breast cancer seeks to fill some gaps in our knowledge about family communication by addressing the following research questions:

27. See McCroskey & Richmond, *supra* note 24, at 31.

28. See COLLINS O. AIRHIHENUWA, *HEALTH AND CULTURE: BEYOND THE WESTERN PARADIGM* 3 (1995).

29. See Anita P. Jackson & Susan J. Sears, *Implications of an Africentric Worldview in Reducing Stress for African American Women*, 71 J. COUNSELING & DEV. 184, 186 (1992).

30. See Judith N. Martin et al., *Conversational Improvement Strategies for Interethnic Communication: African American and European American Perspectives*, 61 COMM. MONOGRAPHS 236, 237 (1994).

31. See Chanita Ann Hughes, *Genetic Testing for Inherited Breast-Ovarian Cancer Susceptibility: The Role of Communication and Personality Characteristics*, 62, 64-65 (1997) (unpublished Ph.D. dissertation, Howard University) (on file with the Department of Psychology, Howard University).

32. See *id.* at 65.

33. See *id.*

(1) Among carriers and noncarriers of BRCA1/2 mutations, what are the rates of self-reported disclosure of BRCA1/2 test results to different family members?; (2) Are women more likely to disclose their BRCA1/2 test results than are males?; and (3) What are the psychological consequences to the proband of disclosing BRCA1/2 test results to family members? The first two of these questions are addressed in a family-based study of BRCA1/2 testing, conducted in collaboration with Dr. Henry Lynch at Creighton University. The third question is addressed in a clinic-based study conducted at the Lombardi Cancer Center at Georgetown University Medical Center.

B. Study #1: A Family-Based Study of BRCA1 and BRCA2 Testing

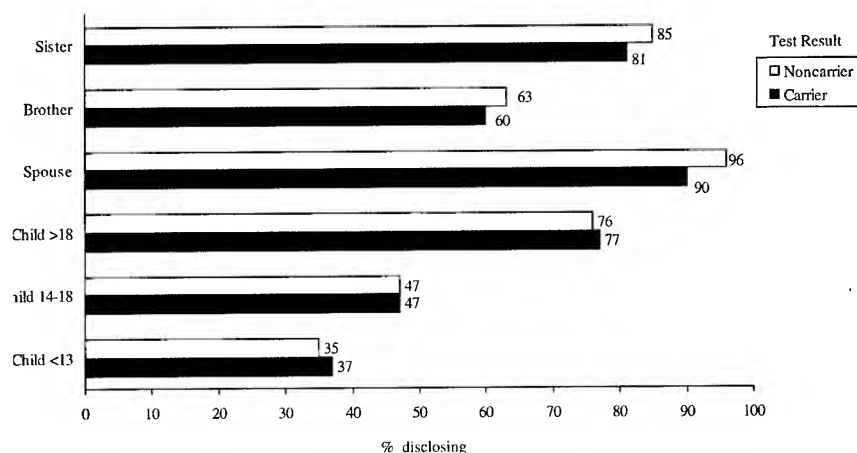
In this prospective cohort study, eligible participants are male and female members of hereditary breast cancer families who participated in earlier genetic linkage studies contributing to the isolation of the BRCA1/2 genes. Consequently, the pedigrees had been completed as part of the earlier research and the contact information on all family members was available. Thus, in contrast to most clinic-based studies, the proband is not placed in the position of providing contact information for other relatives at the time of study entry.

The current study was conducted on a family by family basis. First, letters of introduction were mailed to family members to inform them that the breast cancer susceptibility gene in their family had been identified and that genetic counseling and testing are now available. Consenting family members were asked to participate in a baseline telephone interview to assess demographic characteristics, risk factors, and psychosocial well-being. Individuals interested in genetic counseling and testing had the opportunity to participate in a pre-test education session; most of these sessions were conducted with the extended family. Those who elected to receive their BRCA1/2 test results did so after completing additional written consent forms and participating in individual genetic counseling. In this study, we are following mutation carriers, noncarriers, and decliners of BRCA1/2 testing for a one-year period to evaluate the psychosocial and medical impact of testing. The data on family communication presented here are based on the one-month follow-up assessment.

The frequencies for self-reported disclosure of BRCA1/2 test results among 201 carriers and noncarriers of BRCA1/2 mutations are shown in Figure 1. Overall, rates of disclosure within the first month following testing were quite high. For example, 81% of carriers disclosed their results to a sister and 60% disclosed to a brother. The rates of disclosure to minor children were surprisingly high, consider-

ing the fact that there are no immediate medical implications for young children.³⁴ Seventy-seven percent of carriers disclosed to an adult child, 47% disclosed to a child age fourteen to eighteen and 37% disclosed to a child under age thirteen.

FIGURE 1. FAMILY DISCLOSURE OF BRCA1/2 TEST RESULTS BY CARRIER STATUS

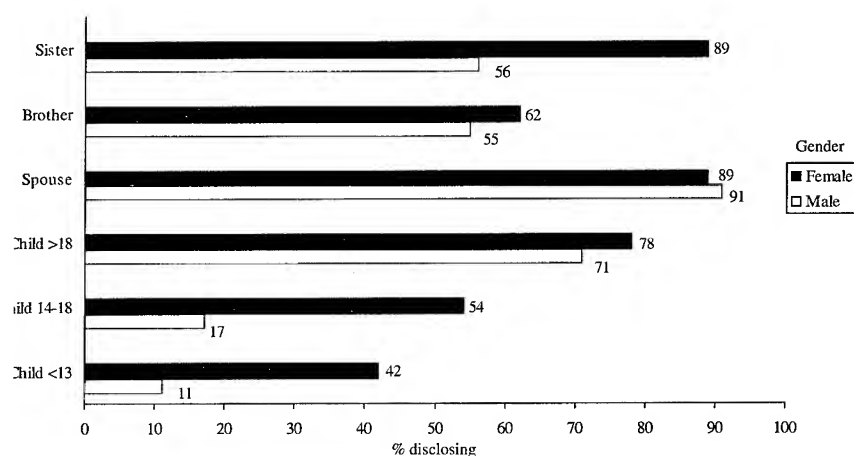


With respect to gender differences, self-reported rates of disclosure of test results among eighty-nine male and female mutation carriers are shown in Figure 2. Female carriers were more likely than males to disclose to a variety of family members. This was especially true for disclosure to sisters (89% of females versus 56% of males) and disclosure to children ages fourteen to eighteen (54% of females and

34. But see Ann-Marie Codori et al., *Genetic Testing for Cancer in Children: Short-term Psychological Effect*, 150 ARCHIVES PEDIATRIC ADOLESCENT MED. 1131 (1996); F.J.M. Grosfeld et al., *Psychological Risks of Genetically Testing Children for a Hereditary Cancer Syndrome*, 32 PATIENT EDUC. & COUNSELING 63, 64 (1997). These studies address genetic testing for conditions such as familial adenomatous polyposis, which can be associated with colon cancer in adolescents, and multiple endocrine neoplasia type 2A, which is associated with a serious form of thyroid cancer, for which prophylactic surgery in children is a consideration. See generally Codori et al., *supra*; Grosfeld et al., *supra*. In general, both studies concluded that there may be significant benefits to offering testing to children for predisposition to these disorders. See generally Codori et al., *supra*; Grosfeld et al. *supra*. There are other rare cancer predisposition syndromes for which it may be appropriate to test children, but the major reason for testing children is when there is an immediate medical benefit. See The American Society of Human Genetics Board of Directors and The American College of Medical Genetics Board of Directors, *ASHG/ACMG Report: Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents*, 57 AM. J. HUM. GENETICS 1233, 1234-36 (1995). In addition, the potential psychological harm must be weighed against the possible benefits. See *id.*

17% of males). One interpretation of these findings is that women are more comfortable communicating about health issues and dealing with the emotional sequelae of disclosure of a positive result. From a social perspective, it is not uncommon for women to take more of the responsibility for caretaking within the family.³⁵ It is also possible that the female spouses of the male mutation carriers in this study had disclosed the results to family members. However, these data are not available at the present time.

FIGURE 2. DISCLOSURE OF BRCA1/2 TEST RESULTS BY GENDER: CARRIERS ONLY



The results also indicated that the effects of carrier status (i.e., BRCA1/2 positive or negative) on disclosure varied by gender. For example, among males, noncarriers were more likely than carriers to disclose results to their sisters (78% versus 56%, respectively). By contrast, in females, the rate of disclosure to sisters was uniformly high (88%) and did not differ based on carrier status. The same pattern emerged for disclosure of BRCA1/2 test results to children. Among males, 33% of noncarriers and 17% of carriers disclosed their test results to a child age fourteen to eighteen. Among females, 53% disclosed to such a child, and there was no effect of carrier status on disclosure. Thus, it appears that men may be more comfortable sharing good news than bad news with other family members.

35. See Martin Richards, *Families, Kinship, and Genetics*, in *THE TROUBLED HELIX: SOCIAL AND PSYCHOLOGICAL IMPLICATIONS OF THE NEW HUMAN GENETICS* 249, 258 (Theresa Marteau & Martin Richards eds., 1996).

We also found that the likelihood of disclosing positive results with young children decreased as the education level of the participant increased. For example, 100% of carriers with less than high school education disclosed their results to a child age fourteen to eighteen, compared with 58% of high school and college graduates and 30% of participants with post-graduate education. To the extent that education level correlates with knowledge, we might interpret this to mean that increasing knowledge of the complexities and risks of disclosure (particularly to children) might dissuade some participants from disclosing to young children.

C. Study #2: A Clinic-Based Study of BRCA1 and BRCA2 Testing

As a result of their prior participation in genetic studies, the participants in the family-based study described above were more aware of the issues and complexities involved in genetic testing than most clinical populations. Further, counseling was performed on a family basis, thereby minimizing the disclosure burden to initial probands. Therefore, as a point of comparison, we are conducting a prospective cohort study of the outcomes of BRCA1/2 testing in the clinical setting. The study design is similar to that described above for Study #1, except that the testing process flows through the initial proband who is the gateway for providing access to other family members (after the proband's results are obtained, and if the result is positive). Further, all counseling and testing is conducted on an individual, rather than family, basis.

Despite differences in the method of ascertaining families, the rates of family disclosure in the clinic-based study were very similar to those for the family-based study. For example, about 81% of carriers and noncarriers disclosed to sisters and 45% disclosed to brothers. However, disclosure to children occurred less frequently in this setting and was more common among noncarriers than among carriers. For example, 40% of noncarriers disclosed their test results to a child age fourteen to eighteen as compared to 14% of carriers. Further, 21% of noncarriers disclosed to a child under age thirteen as compared to 9% of carriers. This suggests that some genetic testing participants may be motivated to disclose negative results for the purpose of reassuring their children.

With regard to the psychological impact of disclosure on the proband, the outcome appears to depend on the object of the disclosure. For example, BRCA1/2 carriers (mostly females in this study) who disclosed their result to their sister exhibited a small decrease in psychological distress, while those who elected not to tell exhibited a

small increase. This difference in trend was both statistically and clinically significant. Thus, this finding suggests that sharing a positive test result with a sister may initially have a positive effect on quality of life. This may be attributable to the fact that the proband fulfills a perceived responsibility to share information that could be medically significant to a close relative, and/or the fact that the proband may obtain emotional support from the relative.

By contrast, the reverse pattern was observed in the context of disclosure of positive test results to young children. In this case, probands who did not disclose their positive test results experienced reductions in distress, while those who did disclose experienced significant increases. Although preliminary, it is tempting to speculate that disclosure to young children may generate, rather than alleviate, psychological distress in carriers. Guilt about transmitting risk to one's offspring may be exacerbated by such discussions.

V. CASE STUDIES OF FAMILY DISCLOSURE IN THE CLINICAL RESEARCH SETTING

The concepts and results presented above are elucidated further by three case studies of the processes and outcomes of family disclosure of BRCA1/2 test results within the clinic-based study described above. These vignettes are based on actual cases but have been modified to protect privacy.

A. *Case #1: All in Good Time*

Ann is a fifty-five year old married Caucasian woman who tested positive for a BRCA1 alteration. Her medical history is significant for bilateral breast cancer diagnosed in her forties, for which she underwent mastectomies. She had her ovaries and uterus removed in her fifties as a preventive measure. Her mother died from ovarian cancer in her forties, and one of Ann's daughters had breast cancer at age thirty. Ann has two other adult daughters and an older brother and sister, none of whom has a history of cancer. Her siblings have adult sons and daughters. She also has several maternal cousins who are at risk for inheriting this alteration.

For Ann, there are few medical implications of this test result. However, there are several relatives who may now be tested. If found to carry this alteration, they would face increased risks for breast and ovarian cancer in women, and prostate cancer in male relatives.³⁶ During the initial pre-test genetic counseling session, Ann expressed

36. See Easton et al., *supra* note 1, at 265; Ford et al., *supra* note 1, at 692.

interest in testing to contribute to breast cancer research and also to gain information for her family, especially her daughters. Prior to obtaining her test results, Ann was concerned about the family's reaction to her results should she test positive, and acknowledged that, as a parent considering implications to her young adult daughters, she would harbor potential feelings of sadness, guilt, and even anger if she tested positive. She had only very limited discussions with her family about her decision to pursue testing. Of particular concern to her were the limitations in available screening and prevention options and how the information might affect her daughters' future childbearing decisions. Although she recognized the difficulty in communicating this information with her family, and the potential for significant emotional distress, she felt strongly about the importance of sharing this information.

When Ann received genetic counseling regarding her positive results, implications to family members were discussed in addition to exploring her own reactions and feelings. Of note, she was counseled that her daughter with breast cancer was very likely to carry this alteration, though Ann was not planning to share the information with her right away. The two individuals with whom Ann shared her results most immediately were her minister and her sister. Her sister was interested in testing and their discussions heightened Ann's concerns about the potential for insurance discrimination, as individuals without a prior history of cancer often have somewhat different worries about how their insurers will handle this type of "pre-existing" condition. She also began to explore with her sister issues related to the dissemination of this information to the rest of the family. Ann's sister had concerns about her own children learning about their aunt's test result.

Ann decided to defer discussion about her results with many relatives. For example, she decided not to disclose to her brother because he was having chronic medical problems. She also decided not to disclose to her daughter with breast cancer because she was undergoing chemotherapy, or to her two other daughters, one of whom was newly married and one of whom was pregnant. Ann clearly perceived the latter two events as happy occasions, and believed that news about her test result could wait until a more appropriate time. Within a year, she shared the information with all her daughters and her brother. Ann also contacted by phone some of her cousins with whom she had a relationship, but was not interested in contacting cousins with whom she had not seen or spoken to in many years. Eventually, her brother and sister were tested, but all of her daughters have declined testing at

the present time. Ann is undergoing counseling now to address her and her family's experiences with cancer and genetic testing, as well as other interpersonal issues.

Analysis: Although some individuals are highly motivated to pursue testing for the sake of family members and to share test results with these relatives, established patterns of communication within the family and the occurrence of other life circumstances are likely to influence how, when, and with whom test results are discussed.

B. Case #2: Don't Ask, Don't Tell

Deborah is a fifty-four year old married Caucasian woman who tested positive for a BRCA2 alteration. Her medical history is significant for unilateral breast cancer diagnosed at age fifty-two for which she underwent breast conserving surgery (lumpectomy), followed by radiation and chemotherapy. Her sister had breast cancer in her mid-fifties, and there is a very strong family history of cancer on their father's side of the family, including breast cancer in two aunts, male breast cancer, pancreatic cancer, and ovarian cancer. With the exception of Deborah, all individuals in the family with a diagnosis of cancer have died. Deborah has three children in their twenties and several nieces in their thirties who she thought would probably be interested in genetic testing. She also has numerous cousins who are also at risk. Prior to learning her test results, Deborah had informed several relatives that she had obtained genetic testing and alerted them to the approximate time in which she would receive her results.

Upon learning her results, Deborah expressed "relief" at finally learning why she developed cancer. Unlike the previous case, these results could have significant medical implications for herself as well as her family. Deborah learned that she was at increased risk for developing another breast cancer (in her affected and opposite breast) and that she also faced an increased risk of ovarian cancer and possibly pancreatic cancer.³⁷ She was counseled about options for early detection (e.g., frequent screenings for breast cancer, blood tests, and

37. See Ford et al., *supra* note 1, at 693 (describing the risks of contralateral breast cancers in BRCA1 carriers estimated at 64% by age 70); Kenneth Offit, *BRCA1: A New Marker in the Management of Patients with Breast Cancer?*, 77 *CANCER* 599, 600 (1996) (discussing the possibility that women with BRCA1 and BRCA2 alterations may also be at risk for ipsilateral breast cancer and the potential impact on management decisions). It is likely that contralateral breast cancer risks are elevated in BRCA2 carriers as well. See Offit, *supra*, at 600; see also Wooster et al., *supra* note 1, at 790; Struwing et al., *supra* note 1, at 1401; Catherine M. Phelan et al., *Mutation Analysis of the BRCA2 Gene in 49 Site-Specific Breast Cancer Families*, 13 *NATURE GENETICS* 120, 121 (1996) (discussing other cancers associated with BRCA2 alterations including pancreatic cancer).

ultrasounds for ovarian cancer) and risk reduction (e.g., use of Tamoxifen, a medication that may reduce the risk of another breast cancer; removal of her breasts and/or ovaries).³⁸ Although Deborah was concerned about these risks, she opted not to alter her medical management and believed that the other measures she employed to stay healthy, such as having a low fat diet and exercising, were sufficient and provided psychological benefits. She felt healthy and wanted to live with as few reminders of her cancer or her cancer risk as possible.

With respect to communication of her test results, within the first several weeks of learning her results, Deborah shared the information with her husband and a co-worker. She had also dropped hints about having her results to various family members including her children, and some of her nieces and cousins. She reported that none of these individuals inquired further as to what the results were or what the implications to them might be. Her feeling was that if they did not ask her directly for the information, she would not share it. She commented that as her children and nieces were young adults, there was no urgency to share this information, though she was counseled that women who have a BRCA2 alteration may face increased risks for breast and ovarian cancer even in their twenties and thirties. Because her result did not significantly change her medical management, she thought it was likely that it would not significantly impact others. She also feared that if relatives did get testing, they would associate testing positive with a "death sentence." Although she was aware that these relatives have a 50% chance of not having the alteration, and that learning such information could provide a substantial amount of reassurance about their cancer risks, she was more focused on the possibility of their testing positive. Through subsequent discussions with the counselor, Deborah revealed that at times, she felt somewhat guilty about "withholding information" from her family. One strategy for addressing this issue was to role play different language that could be used to disclose the information and to imagine the relatives' reaction along with her response.

It has been over a year since Deborah obtained her results, and no relatives have been notified of this information. Deborah believes that with time, her feelings about communicating her result may change, for example, as her children get older or as they consider having children. If there are changes in Deborah's own history or her

38. See Burke et al., *supra* note 1, at 997.

family history of cancer, these events may also affect her feelings about sharing the information.

Analysis: Individuals' beliefs about the impact of test results for themselves may affect their perception of how or whether others will utilize the information, or when they should be notified of the information. The health care providers informed Deborah about who is at risk and offered to facilitate communication with these relatives about the availability of genetic counseling with the option of testing, but were respectful of her wishes not to share the information. In order for individuals to feel comfortable pursuing testing, they must know that researchers and clinicians will handle the information responsibly and respect their autonomy and decision process.

C. Case #3: A Family Affair

Margaret is a sixty-five year old married Caucasian woman who tested positive for a BRCA1 alteration. She had a history of breast cancer at age forty-five, for which she underwent a mastectomy of her affected breast and a preventive mastectomy of her opposite breast. Her family history is notable for two sisters with early onset breast cancer, one of whom also had ovarian cancer and was getting treatment for metastatic ovarian cancer at the time. Margaret also has two sisters and two brothers who have never had cancer. Their mother was diagnosed with breast cancer at age fifty. All of her siblings have adult children, and she has three daughters. Margaret sought genetic testing. She was initially interested in testing to learn about her risk for ovarian cancer and also to gain information for her family. Within six months of learning her results, Margaret opted to have her ovaries removed—a decision influenced by her sister's battle against ovarian cancer.

It was clear from the first meeting with Margaret that she assumed a matriarchal role in this family and that the family was very close. They were also united in family crises, such as the recent death of Margaret's husband and her sister's illness. Within a few months, all of her siblings participated in a group pre-test counseling session (per their request), along with Margaret, and openly shared their hopes and concerns regarding testing. They received their results individually, and all reported that they shared their results, regardless of the outcome, with their children. Some of those children later opted for testing. Margaret's daughters also opted for group counseling, and all received testing. Margaret and her siblings were interested in having the clinical research team assist them in contacting more distant relatives, such as great aunts and uncles and cousins, to invite

them to participate in a free genetic counseling clinical research program. Some of these individuals did participate and were aware of Margaret's experiences, and looked to her for information and support, as did the rest of the family. During follow-up calls, family members often shared their feelings about how relatives were coping with the information. Although subjective, this information allowed the counselor to gain insight into the type of added support or information that could be offered. Margaret's involvement was instrumental in helping the family benefit from genetic counseling, regardless of whether or not they chose to get tested or what their result was if they did get testing.

Analysis: In families that are close-knit, open, and have established lines of communication, the transmission of information about genetic test results may flow with relative ease. Individuals in these families often rely on each other for information, support, and advice about medical decision-making. Furthermore, the individual who initiates testing in such highly motivated families may be central in these activities. These important roles are often beyond the scope of what the counselor is able to provide. However, because there is concern that family members may feel somewhat pressured into getting genetic testing and making certain subsequent decisions, it is incumbent upon the counselor to ensure that individuals are aware of the full spectrum of benefits, limitations, and risks of testing before they decide whether to get tested. The counselor should also be available to help them assimilate and cope with the information.

VI. SUMMARY AND IMPLICATIONS

The quantitative and qualitative (case studies) data presented in this paper have implications, not only in the health care context, but also in the legal arena. The results of both a family-based and clinic-based approach to genetic counseling indicate that the vast majority of genetic counseling participants opted to disclose their test results to immediate adult family members. Consistent with previous research,³⁹ most of these individuals elected to share the information themselves, rather than have the information disclosed by counselors or other health care providers. Complex psychological and medical issues influenced the decision to disclose, as well as the timing and mode of disclosure. Clinicians and researchers should be sensitive also to cultural influences involved in decisions about family disclosure.

39. See Sorensen et al., *supra* note 22, at 421.

Thus, the ability to control the process of disclosure is of great importance to genetic counseling participants. This raises a variety of concerns about the disclosure of genetic information by other sources, such as healthcare providers, insurance companies, or government institutions. From a legal standpoint, the obligations and authority of other sources in disclosure of genetic information is far from clear. For example, two recent legal cases have rendered differing opinions about a physician's responsibility to inform relatives about their risk of developing a genetic disease. The first of these, *Pate v. Threlkel*,⁴⁰ concluded that the physician had a duty to warn the patient about the genetic nature of the disease and that the patient could then be expected to warn their family members.⁴¹ It was also stated that disclosure laws would prohibit the physician from warning other family members.⁴² The second case, *Safer v. Pack*,⁴³ reached a differing conclusion. In this case, it was decided that the physician did have a duty to inform the family of their risk of developing a genetic disease.⁴⁴ The second case is obviously at odds with both the physician's duty to protect patient confidentiality and with the explicit desires of patients to control the diffusion of their personal genetic information. While this apparent conflict is far from settled, a recent analysis suggests that health care providers have a responsibility to at least inform patients about the implications of their test results to relatives and to encourage (but not advise) patients to share this information.⁴⁵ In addition, the American Society of Human Genetics recently published a statement maintaining that "genetic information should be considered as medical information" and further outlining the "exceptional" circumstances under which a health care provider should have a discretionary right to disclose genetic information to at-risk family members.⁴⁶ It is not clear from this statement whether disclo-

40. 661 So.2d 278 (Fla. 1995).

41. *See id.* at 282.

42. *See id.*

43. 677 A.2d 1188 (N.J. Super. Ct. App. Div. 1996), *cert. denied*, 683 A.2d 1163 (N.J. 1996).

44. *See id.* at 1192.

45. *See* Benjamin S. Wilfond et al., *Cancer Genetic Susceptibility Testing: Ethical and Policy Implications for Future Research and Clinical Practice*, 10 J.L. MED. & ETHICS (forthcoming 1998).

46. *See* The American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, *ASHG Statement: Professional Disclosure of Familial Genetic Information* 62 AM. J. HUM. GENETICS 474, 474 (1998) (discussing that a provider may be permitted to disclose genetic information "where attempts to encourage disclosure on the part of the patient have failed; where the harm is highly likely to occur and is serious and foreseeable; where the at-risk relative(s) is identifiable; and where either the disease is preventable/treatable or medically accepted standards indicate that early monitoring will reduce the genetic risk"

sure of BRCA1/2 test results would fall under this purview.⁴⁷ However, even with these considerations, the possibility that government institutions or insurance companies could order and disclose such information poses even greater threats to patient confidentiality and well-being.

The data presented herein also show that females are significantly more likely to disclose genetic information to their relatives, especially when test results are positive and when the relatives are minor children. A particular concern is that such patterns of disclosure may place females at greater risk in the context of family law disputes.⁴⁸ For example, it is conceivable that information about a positive mutation status and elevated cancer risk could be used against female mutation carriers in custody disputes or adoption proceedings.⁴⁹ This possibility underscores the importance of informing counseling participants about a myriad of potential risks associated with family disclosure beyond the medical and psychosocial risks that are typically addressed.

Although preliminary, other findings from our research suggest that both disclosure and nondisclosure of positive test results to relatives may result in increased psychological distress for the discloser, and possibly for the relatives with whom this information is shared, although data on the latter are not available. Thus, in addition to informing and counseling patients about the medical and legal risks noted above, providers may have an obligation to review the potentially adverse psychological effects of family disclosure. It is arguable that such information should be considered an essential component of the informed consent process which takes place prior to the provision of a blood sample for genetic testing and which is reinforced when results are disclosed.

In the coming years, as genes for several common multiple adult-onset conditions are identified, many more individuals will have the opportunity to learn what their future may hold, and will then have to address the inevitable familial implications of this knowledge. Given the complexities of the medical decision making and psychological adjustment associated with genetic testing, it is hoped that an under-

or where "[t]he harm that may result from failure to disclose should outweigh the harm that may result from disclosure").

47. *See id.* at 474-83.

48. Telephone Interview with Karen H. Rothenberg, Marjorie Cook Professor of Law and Director, Law and Health Care Program, University of Maryland School of Law (January 7, 1998).

49. *Id.*

standing of the unique determinants and consequences of disclosure to family members can help clinicians provide better counseling to these individuals and will encourage legislators to enact and enforce protections for patient autonomy and confidentiality. This strategy will help ensure that individuals who decide to pursue genetic testing, even in the context of its uncertainties, can obtain maximum benefit while the potential for harm is minimized.

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Cancer Assessment and Risk Evaluation

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CARE Program Overview

The CARE (Cancer Assessment and Risk Evaluation) Program is a genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. This is a free program that is supported primarily by a research grant from the National Human Genome Research Institute, (a division of the National Institutes of Health), and the National Cancer Institute. Additional funding is provided by the Department of Defense and the Susan G. Komen Foundation.

Participation in CARE

Through the CARE Program, each participant meets with a genetic counselor or nurse educator to discuss:

- *a detailed family history and risk factor assessment*
- *the genetics and inheritance of breast and ovarian cancer*
- *personalized guidelines for cancer prevention and screening*
- *the options available for genetic testing for cancer susceptibility, including the pros and cons of testing (genetic testing is offered to all eligible individuals)*

The CARE program is a clinical research program. One of the goals of this research is to determine the best methods of education and counseling about genetic testing for breast and ovarian cancer risk. Therefore, women who are found to have an altered BRCA1 or BRCA2 gene may be assigned randomly to one of two genetic counseling programs: (1) standard genetic counseling or (2) standard genetic counseling plus follow-up psychosocial telephone counseling. All participants are asked to complete telephone and in-person interviews and questionnaires both before and after participation. These assessments are important to evaluate the benefits of the program, and will help us learn more about how people make decisions about genetic testing and about the impact of these decisions on their lives. We are also exploring the impact of genetic testing on family members. In addition, we are studying questions of clinical importance for those individuals who learn that they have an alteration in the BRCA1 or BRCA2 gene, such as factors that modify risk, and the effectiveness of screening and prevention options.

CARE Staff

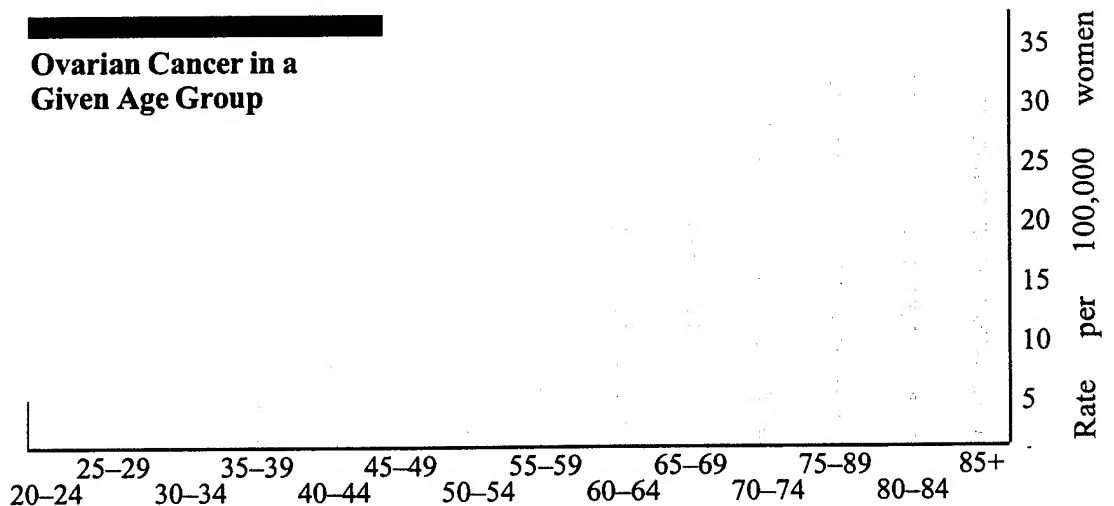
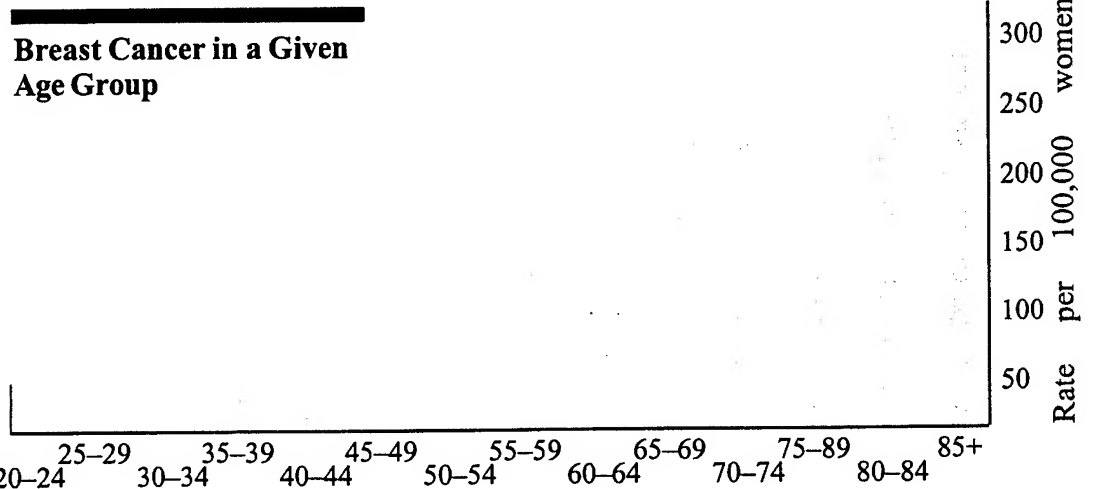
The clinical staff of the CARE program includes two master's level genetic counselors, a master's level nurse educator, and a medical director—a physician trained in medical oncology. The principal investigators of the CARE program are clinical and behavioral psychologists. These individuals work closely with other oncologists, surgeons, nurses, and psychologists at Georgetown University Medical Center to provide services and information to CARE participants.

Major Risk Factors for Breast and Ovarian Cancer

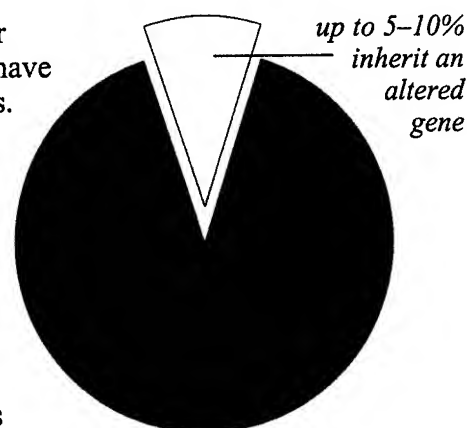
All women have a risk of developing breast and ovarian cancer over their lifetimes. Breast cancer is a common disease, with over 175,000 women diagnosed every year in the United States. Ovarian cancer is a much rarer disease, which is newly diagnosed in about 25,000 women annually.

The cause of these diseases cannot be pinpointed to a single factor. Breast and ovarian cancers result from a combination of genetic (inherited) and environmental (non-inherited) factors. Key risk factors for breast and ovarian cancer are summarized below.

Age: A woman's age is the most significant risk factor for getting breast or ovarian cancer. The older a woman is, the higher her risk of developing breast or ovarian cancer. At least three-fourths of breast and ovarian cancers are diagnosed in women over the age of 50, as noted on the charts below. However, women with an inherited predisposition to breast and ovarian cancer face an increased risk of developing these cancers at younger ages, such as in their 30s and 40s.



Family history: The risk of developing breast or ovarian cancer is higher among women who have one or more close relatives with these cancers. The risk may be increased further if the cancers were diagnosed at a young age, especially before menopause, or if breast cancer occurred in both breasts. Although many women with breast cancer have a close relative with this disease, only about 5–10% of women are thought to have an inherited susceptibility to cancer. Because ovarian cancer is much rarer, familial clusters are less common. A family tree constructed by the genetic counselor is a useful tool to help determine whether an individual's family history is suggestive of an inherited pattern of cancer predisposition.



Biopsy history: Most breast lumps, often called “fibrocystic disease,” are benign (not cancerous). However, a breast biopsy that shows the growth of altered cells (known as atypical hyperplasia) is associated with an increased risk of developing breast cancer. This risk is increased further if a woman has a close relative with breast cancer.

Prior cancer history: Any woman who has a prior history of breast cancer has an increased risk of developing a second breast cancer (for example, in her opposite breast after a mastectomy). Women with a prior history of breast cancer also have a slight increased risk for ovarian cancer. These risks are significantly higher if a woman is found to have an alteration in a gene such as BRCA1.

Other Risk Factors for Breast and Ovarian Cancer

In addition to a woman's age, history of breast biopsies or cancer, and family history, other factors may contribute to a woman's risk for developing breast or ovarian cancer. It is important to understand that for women with an inherited predisposition to breast or ovarian cancer the extent to which the risk factors below may affect risk is largely unknown. Studies are underway to address these issues.

Reproductive factors:

Hormonal changes related to menstruation and pregnancy may increase a woman's risk for breast cancer. These include having menstrual periods before age 12, menopause after age 55, never having children, or giving birth to a first child after age 30. A woman who has never given birth also has an increased risk for ovarian cancer.

Oral contraceptives:

The use of the pill, or oral contraceptives (OCs), is not associated with a significantly elevated risk of breast cancer, although long-term use of OCs in women under age 25 may be associated with a slight increase in the risk of developing breast cancer at a young age. However, even short-term (i.e., 6 month) use of OCs may reduce the risk of ovarian cancer.

Hormone replacement therapy:

Studies have demonstrated that long-term hormone replacement therapy (HRT), with estrogen alone or estrogen and progesterone, slightly increases breast cancer risk. It is important to remember, however, that estrogen replacement therapy may also provide other health benefits such as relief of menopausal symptoms, and protection from cardiac and bone disease (i.e., osteoporosis).

Other factors:

Based on current information, there is no evidence that high amounts of fat in the diet increase the chance of developing breast cancer; however, reducing fat in the diet can reduce the risk of other diseases and cancers. Alcohol consumption is also associated with a slight increase in breast cancer risk, and appears to be related to the amount consumed over a period of years.

Inheritance of Cancer Susceptibility

In order to better understand how an individual may inherit a susceptibility to cancer, it is helpful to know some basic concepts in genetics.

Chromosomes:

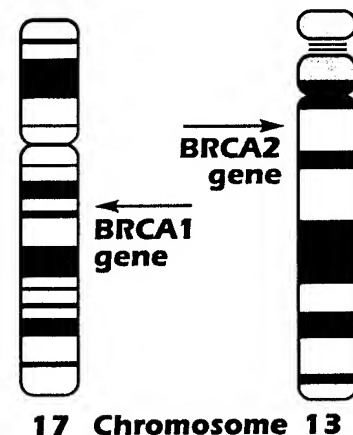
Chromosomes are found in the nucleus or control center of a human cell and are the structures on which genes are located. There are 46 individual chromosomes, or 23 different pairs, in each cell. The chromosomes are passed down, or inherited, randomly from parent to child; 23 chromosomes are passed down from the mother and 23 chromosomes are passed down from the father. Since our chromosomes are found in pairs, the genes they contain are also found in pairs.

Genes:

There are approximately 50,000 to 100,000 genes in a human cell. Genes are the blueprints or instructions that control the growth, development, and normal function of the body. Only a small proportion of our genes is associated with cancer susceptibility.

When genes are working properly, our bodies are able to develop and function smoothly. However, when a gene is altered (e.g., by the addition, deletion, or rearrangement of genetic material), a normal cell function, such as cell growth, may be impaired or changed.

Thus, in some instances, altered genes may result in a deformity or the development of disease. An altered gene may also result in very subtle effects. In fact, it is estimated that each individual has several altered genes that have no noticeable effects.



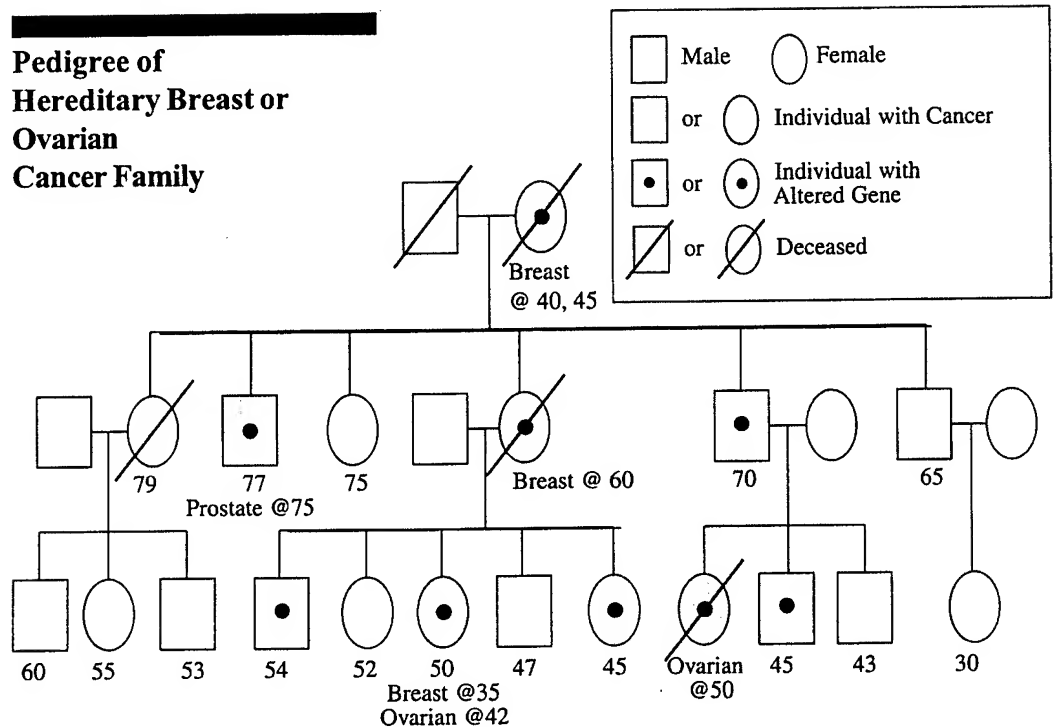
17 Chromosome 13

Dominant Inheritance:

Often, the way that cancer susceptibility may be passed down in families is by dominant inheritance. People have two copies of every gene (one copy from each parent). Both copies of a gene pair control the same function but may vary in form from each other, since each copy is received from a different parent. An alteration or change in one copy of a gene pair can affect how the body functions even though the other copy of that gene may not be altered. In this situation, the altered gene tends to dominate over the working gene, which impairs the function of the gene. Alterations in BRCA1 and BRCA2 are inherited in a dominant fashion.

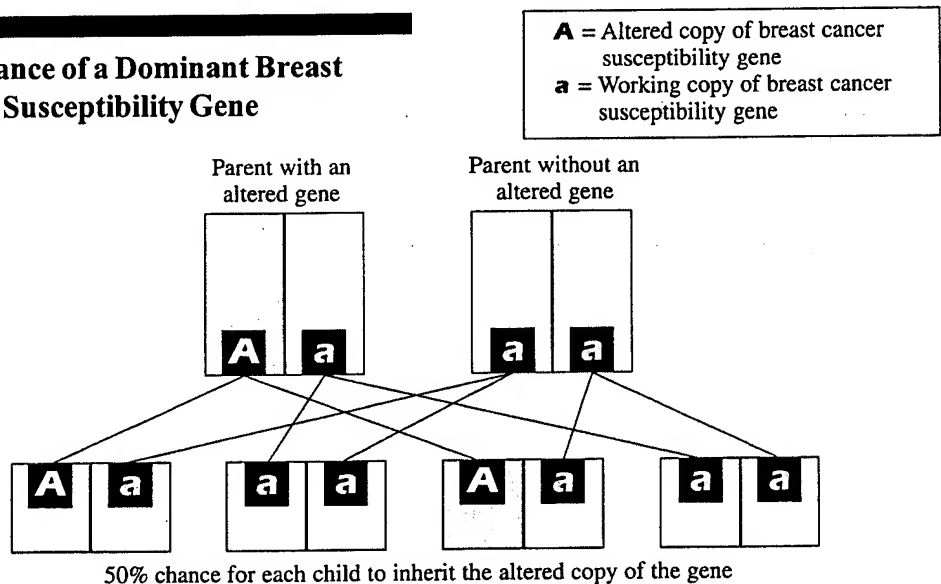
In large families, this inheritance pattern may be observed clearly because there are multiple individuals in several generations affected with breast and/or ovarian cancer, often at young ages. The family tree on the following page depicts dominant inheritance of a cancer susceptibility gene, showing individuals who have inherited the altered gene, and whether they have developed cancer.

**Pedigree of
Hereditary Breast or
Ovarian
Cancer Family**



An individual with a BRCA1 or BRCA2 alteration has a 50% chance of passing down that alteration to his or her children. This happens because eggs and sperm each carry only one copy of each gene pair. Thus, each child of a parent with an altered gene has a 50% chance of inheriting the altered gene and a 50% chance of inheriting the functioning gene (see below). The risk is not affected by the sex of the child or the affected parent, or by the child's birth order, and cannot be predicted based on how much a child may resemble one or the other parent.

**Inheritance of a Dominant Breast
Cancer Susceptibility Gene**



Breast Cancer Susceptibility Genes

BReast CAncer-1 (BRCA1) and BReast CAncer-2 (BRCA2) are the two major breast cancer susceptibility genes that have been identified to date. Alterations in these genes are thought to account for the majority of inherited breast and ovarian cancers. The frequency of these altered genes in the general population is not known, but one estimate suggests that BRCA1 alterations occur in up to 1 of every 800 individuals in the general population and BRCA2 alterations appear to be even more rare.

The BRCA1 and BRCA2 genes are thought to act as “tumor suppressor” genes when they are functioning properly. Tumor suppressor genes prevent cells in our body from growing out of control. However, alterations of these genes can change their usual function. This change in function can increase a person’s chance of developing breast, ovarian, and some other cancers.

As the BRCA1 and BRCA2 genes are very large, there are many places within each gene where an alteration (mutation) can occur. More than 300 alterations have been identified in individuals of all racial and ethnic groups. However, some mutations occur much more frequently than others in specific populations. For example, a study of over 5000 Ashkenazi (Central or Eastern European) Jewish individuals in the Washington, DC area revealed that about 1 in 44, or 2.3%, of the participants carried one of three alterations in the BRCA1 or BRCA2 genes. Specifically, the alterations are referred to as 185*del*AG and 5382*ins*C in the BRCA1 gene and 6174*del*T in the BRCA2 gene. The notation refers to the place in the gene where some material was *deleted* or *inserted*. In addition, a specific mutation in the BRCA2 gene known as 999*del*5 seems to account for nearly all the cases of hereditary breast cancer in Iceland. Some alterations have also been found more commonly in French Canadians, Swedes, Norwegians, and African-Americans.

Research is underway to identify and characterize mutations in BRCA1 and BRCA2. This research will lead to more rapid and efficient means of genetic testing, an improved understanding of the cancer risks associated with these alterations, and more information about the function of these genes. Ultimately, these discoveries may lead to improved prevention, early detection, and treatment of cancer.

The Process of Genetic Testing

The process of genetic testing is different from most other medical tests. A genetic test for cancer susceptibility is not diagnostic; that is, it does not reveal the presence or absence of cancer, but whether an individual has an inherited tendency or predisposition to cancer. Also, the methods used in performing genetic analysis are very complex and time consuming. Unlike most routine lab work, results from genetic testing may take several weeks or months to obtain and sometimes results may be difficult to interpret. Another difference is that most of the risks associated with genetic testing are not physical risks, but involve risks associated with how one may feel or how others, including family members, may react after learning about a genetic test result. For this reason, education and counseling before and after testing are offered as part of the CARE program.

A small blood sample is needed in order to perform genetic testing. Genetic material (DNA) is then obtained from your blood and analyzed for alterations (mutations). For a family in which a mutation has not been previously found, it is helpful to first test a blood sample from a woman with breast and/or ovarian cancer who was diagnosed at a young age. Scientists have a number of ways of looking for genetic mutations. In some instances, testing is performed in steps, whereby common mutations in the BRCA1 and the BRCA2 genes are looked at first. If these alterations are ruled out, then more complete analysis of the gene may be undertaken. The most complex type of genetic analysis is called sequencing, which means that the “chemical alphabet” of an individual’s DNA is obtained and compared to DNA that is known to be “normal.” The process of sequencing is comparable to looking for a single spelling mistake in a several thousand-page book—a very difficult and time consuming process. Alterations include those in which some genetic material is missing, substituted, or inserted. In very rare instances, an alteration may be identified that is of questionable clinical significance (in other words, the alteration may represent a normal variation in DNA as opposed to an alteration known to be associated with increased cancer risks). Interpretation of such results is handled on a case by case basis.

Once a clinically significant alteration in the BRCA1 or BRCA2 gene has been identified in a close relative, it is easier to test other individuals in the family. Because the specific alteration in the gene is known, other individuals in the family are usually tested only for the presence or absence of that mutation. This testing can be completed in a relatively short period of time and is very accurate, providing results that are clearly positive or negative for a particular alteration.

If an alteration is not identified in a family member who has had cancer, relatives are usually not tested. In such cases, testing would not be expected to provide further information about an individual’s cancer risks. For example, it may be determined that the first woman to be tested within a family who has had early onset breast and/or ovarian cancer does not have a BRCA1 or BRCA2 alteration. This test result may be due to one of the following possibilities:

- Current methods may not be sensitive enough to detect a mutation in the BRCA1 or the BRCA2 gene (e.g., the mutation may be in a part of the gene that is difficult to analyze).
- A mutation is present in a different cancer susceptibility gene for which testing was not performed. These genes may be rare and/or as yet unidentified.
- The individual(s) tested does not have an inherited susceptibility to cancer due to an alteration in a single gene such as BRCA1 or BRCA2.

Estimated Cancer Risks Associated with BRCA1 and BRCA2 Alterations

The risks for cancer associated with BRCA1 or BRCA2 alterations, summarized in the following table, are based on several disease-conferring mutations.

The available risks are cumulative (lifetime) and are only estimates, derived in part from studies of large families in which multiple women developed breast and ovarian cancer. However, some of the risks are derived from studies in which individuals who were tested were not selected because of a strong family history of breast or ovarian cancer. It is therefore important to note that as additional families are studied, these risks may be modified, although it is unclear by how much these cancer risks may change.

It is also important to remember that risk varies from individual to individual and from family to family, so it is not possible to predict with certainty the type of cancer to which an individual is most susceptible or the age at which the cancer may develop.

Risks of cancer have been derived primarily from studies with Caucasian women, and many studies have focused specifically on risks in individuals of Jewish ancestry. Thus, there is not a lot of specific information about cancer risks in women from different racial/ethnic groups. Therefore, the participation of individuals of diverse backgrounds in the CARE program will contribute substantially to our understanding of hereditary breast cancer. In addition, answering questions regarding your feelings about cancer and genetic testing, even if you decide not to have testing, will help us improve our genetic counseling and education programs.

The table below summarizes estimated lifetime risks for different cancers for individuals with a BRCA1 or BRCA2 alteration as compared to the general population. The discussion that follows covers important points and highlights from the table.

ESTIMATED LIFETIME CANCER RISKS ASSOCIATED WITH BRCA1/BRCA2

Updated September 1999

Type of cancer	BRCA1	BRCA2	General population
BREAST CANCER			
Breast cancer (female)	55%-85%	55%-85%	10%-13%
2nd breast cancer (Same breast)	Possibly increased	Possibly increased	Depends on individual factors
2nd breast cancer (Opposite breast)	Up to 65%	Up to 50%	Up to 0.5% to 1% per year after diagnosis
Breast cancer after ovarian cancer	Increased	Increased	Possibly slightly increased
OVARIAN CANCER			
Ovarian cancer	15%-60%	15%-25%	2%-3% (about twice the average risk)
Ovarian cancer after breast cancer	30%-55%	15%	
OTHER CANCERS			
Colon cancer	Possible increased risk (onset at average age)	No significant increased risk	About 6%
Prostate cancer	Increased risk, possibly by 3-fold	20%-30% (risk may be especially elevated in men less than age 65)	At least 10% but risk is difficult to quantify due in part to the presence of clinically undetectable cancers
Breast cancer (male)	Reported on rare occasions but overall risks not thought to be significantly increased	Approximately 6% (early onset generally not reported)	Extremely rare
Pancreatic cancer	Not increased	1%-5%, with possible early onset	Rare
Other associated cancers	None known	Gallbladder and bile duct Stomach Melanoma	Varied

Breast Cancer:

In general, if a woman has an alteration in either the BRCA1 or the BRCA2 gene, the risk of developing breast cancer over her lifetime is 55-85%. This risk applies to women who have never had a diagnosis of breast cancer, and may vary based on a woman's current age. In addition, early ages of onset for breast cancer have been reported to occur frequently in women with BRCA1 or BRCA2 alterations.

Once breast cancer has been diagnosed, many women wonder what the chance is that they will develop another breast cancer. It is estimated that a woman with a BRCA1 or a BRCA2 mutation has up to a 50 to 65% risk to develop a new breast cancer in the opposite breast. For women in the general population, their risk to develop a second breast cancer in the opposite breast is 0.5 to 1% a year. (Note: These risks are for new cancers. These numbers do not apply to the risk for metastasis, in which the primary cancer spreads from one part of the body to another.)

BRCA1/2 mutation carriers may also have an increased risk of developing breast cancer again in their affected breast (e.g., such as after having a lumpectomy). However, there are limited data available regarding the risk of developing a second cancer in the affected breast. While BRCA1/2 mutation status is a factor in determining the risk for a second breast cancer, other important factors must also be considered. These include type of initial breast cancer, the use of medications such as Tamoxifen, and the choice of surgery.

Ovarian Cancer:

Risks for other cancers, especially ovarian cancer, are elevated in women with a BRCA1 or a BRCA2 alteration. Although early ages of onset for ovarian cancer have been reported in women with BRCA1 alterations, recent data suggest that most women with BRCA2 mutations develop ovarian cancer after age 50.

Cancers in Men:

Males who inherit a BRCA2 alteration have a significantly increased risk of developing prostate cancer, especially under the age of 65. This risk is estimated to be between 20-30%. Men who carry a BRCA1 alteration may also face an increased risk of prostate cancer, but the age of onset does not appear to differ significantly from that of men in the general population. In addition, it is estimated that BRCA2 alterations are associated with a 6% risk for male breast cancer. The overall chance for male mutation carriers to develop breast cancer is small, and usually breast cancer does not affect men at young ages. However, this risk represents a considerable increase over that of the general population, in which male breast cancer is extremely rare. Breast cancer in men with a BRCA1 alteration has been reported on rare occasions. While there is no specific screening available for males at increased risk for developing breast

cancer, it is important that men who carry a BRCA1 or BRCA2 alteration are aware of any changes in their breast tissue and report them to their doctor immediately.

Other Cancers Associated with BRCA2 Alterations:

A recent study showed that both men and women who carried a BRCA2 alteration had increased risks for developing other cancers. However, the risk levels were much lower than those observed for breast, ovarian, and prostate cancer, and were overall quite low. For example, the study found that there was a lifetime risk of 1-5% for developing pancreatic cancer. Thus, the vast majority of men and women with a BRCA2 alteration did not develop this cancer. Of note, however, previous studies reported that in some cases the age at diagnosis for pancreatic cancer may be younger than that observed in the general population, although additional research is needed to confirm these findings. Other cancer sites associated with BRCA2 include the gallbladder and bile duct, stomach, and skin (melanoma). The study did not show that there was an increased risk for colon cancer associated with BRCA2 alterations, as some earlier studies had suggested. Of these other cancers, melanoma is the only condition for which screening and prevention is readily available (see the section entitled "skin cancer screening"). As there are no proven methods for early detection for the other cancers, screening is not usually performed. However, additional information regarding possible screening options for these cancers is available upon request.

Cancer Screening

At present, there are no long-term studies that have demonstrated the best methods to screen for or prevent cancer in an individual with an alteration in the BRCA1 or the BRCA2 gene. Participants in the CARE program receive individualized guidelines for cancer risk management that should be discussed with their personal physicians. The following summarizes general approaches for early detection of the major cancers associated with hereditary breast and ovarian cancer suggested for consideration by individuals who are found to carry an alteration in the BRCA1 or the BRCA2 gene.

Breast Cancer Screening:

Monitoring for breast cancer includes:

- frequent clinician breast exams
- mammography
- monthly breast self-examination

Women at increased risk for breast cancer may choose to undergo exams at a younger age and more frequently than women in the general population.

Ovarian Cancer Screening:

Women in the general population do not undergo routine screening to detect ovarian cancer. An annual gynecological exam, which should be a part of every woman's care, includes a Pap smear, a test used to detect cancer of the cervix, and a pelvic exam. A pelvic exam is important for detecting some problems, but it is not a sensitive method to detect ovarian cancer. Therefore, for women at increased risk of ovarian cancer, screening involves two tests in addition to pelvic exams: a CA-125 blood test and a pelvic ultrasound with color Doppler enhancement. Although these additional screening tests are available, they have not been proven to detect ovarian cancer in its early stages, when treatment is most effective. In other words, these tests may be abnormal even when no cancer is present, or can be normal when cancer is present.

Colon Screening:

All individuals (men and women) are encouraged to undergo routine screening for colon cancer beginning at age 50. Such exams include digital rectal exams and fecal (stool) blood tests annually, in addition to sigmoidoscopy (an exam of the lower colon) or colonoscopy (an exam of the entire colon), every 3-5 years. It is important to discuss the relative benefits and risks of these procedures with your doctor.

Prostate Screening:

Men should have regular screening for prostate cancer, beginning at age 50, or earlier if certain risk factors exist, such as a family history of prostate cancer. Screening tests for prostate cancer include annual PSA (prostate specific antigen) blood tests and digital rectal exams.

Skin Cancer Screening:

In considering the high frequency of skin cancer, and the association of melanoma with alterations in the BRCA2 gene, it is important to have exams of the skin during regular checkups with a physician. In addition, individuals should check regularly for new growths, sores that do not heal, changes in the size, shape or color of any moles, or any other changes on the skin that should be reported to the doctor right away. It is also important to minimize exposure to the sun and use sunscreen for added protection.

Prevention for Breast and Ovarian Cancer

Prophylactic Surgery:

Some women at increased risk for breast cancer may consider having their breast(s) removed preventively, a procedure known as **prophylactic mastectomy**. This procedure involves the removal of the entire breast, including the skin overlying the breast and the nipple. Because some breast tissue remains after this surgery, there is still a small chance for a woman to develop breast cancer after having prophylactic mastectomy. However, a recent study found that for women with a high risk of breast cancer on the basis of family history, prophylactic bilateral mastectomies reduced the incidence of breast cancer by at least 90%. It is expected that data will become available that address the effectiveness of prophylactic mastectomy specifically in women with a BRCA1 or a BRCA2 alteration.

Due to the limitations of ovarian screening, women at high risk for ovarian cancer may consider having their ovaries removed, especially after childbearing is completed. This procedure is known as **prophylactic oophorectomy**. While this surgery significantly reduces the risk for ovarian cancer, there is still a small chance of developing an ovarian-like cancer after the ovaries are removed. Women who have had this surgery generally do not undergo screening tests for ovarian cancer, but are closely followed by their physicians. A consideration for young (premenopausal) women who decide to have prophylactic oophorectomy is that such surgery may result in early menopause, potentially several years before it would have occurred naturally. As the use of hormone replacement therapy may not be desirable, non-hormonal methods may be available to reduce the symptoms of menopause (see section about hormone replacement therapy). Another important consideration related to prophylactic oophorectomy is that in addition to reducing the risk of ovarian cancer, a recent study indicated that this surgery reduces the risk of breast cancer in women with a BRCA1 alteration who had their ovaries removed prior to age 50. Data regarding BRCA2 are pending, but are likely to be similar. These data do not suggest that oophorectomy should be considered mainly as a means to lower the risk of breast cancer. The primary reason for considering such surgery is related to reducing the risk for ovarian cancer.

It is important to remember that there is no right or wrong decision about getting prophylactic surgery. We know that women who undergo preventive surgery still have residual risks for cancer, and it is possible that women with an inherited susceptibility to breast or ovarian cancer may face a higher remaining risk than women without a genetic predisposition to cancer. There are many other factors to be considered before undergoing surgery, such as the effectiveness of the currently available screening procedures, the type and extent of surgery that would be performed, the emotional impact of surgery, other medical implications and financial costs. Before deciding whether to have surgery, all of these issues should be discussed in more detail with your physicians, which may include oncologists, endocrinologists and plastic surgeons.

Chemoprevention (medications that may reduce cancer risk):**Tamoxifen and other related medications**

Tamoxifen, a hormonal medication, has been used to treat some women who have had breast cancer to prevent the cancer from spreading and to reduce the chance of getting another breast cancer. A recent large study showed that Tamoxifen reduced the risk of breast cancer in women at increased risk for breast cancer (without a prior history of the disease). Tamoxifen use may also be associated with other health benefits and risks. It is not yet known if Tamoxifen lowers the risk of breast cancer in women with a BRCA1 or a BRCA2 alteration. Based on this information, it is not clear whether women with breast cancer who did not receive Tamoxifen for their initial treatment should consider taking Tamoxifen to reduce the risk of a second breast cancer. There is now a clinical trial looking at the effects of Tamoxifen and Raloxifene (a drug used currently to treat osteoporosis and which may reduce the risk of breast cancer) in menopausal women. The trial, conducted at Lombardi Cancer Center and other centers, is called STAR (Study of Tamoxifen and Raloxifene). Lombardi Cancer Center is also conducting a study for high-risk women who may or may not be taking part in the STAR trial. This study is examining novel imaging techniques such as MRI and performing other tests on the breast. Additional information about both of these trials may be obtained by calling the Lombardi CancerLine at 202-784-4000. There is also a clinical trial open for high-risk women who have not gone through menopause. This trial is a study of Raloxifene, a drug used currently to treat osteoporosis and which may reduce the risk of breast cancer. The trial is being conducted at the National Institutes of Health (NIH). For more information or to find out if you can participate, call the Clinical Studies Support Center at NIH at 1-888-624-1937. Your physician can also provide additional information about Tamoxifen and other related clinical trials.

Oral contraceptive use

A recent study showed that women with an alteration in BRCA1 or BRCA2 who used oral contraceptives (OCs) for six or more years reduced their risk of ovarian cancer by 60%. Use of the pill for three years was associated with a 20% risk reduction in ovarian cancer risk. This was the first study to show a significant decrease in ovarian cancer risk for mutation carriers who used oral contraceptives. Further studies are needed to confirm these findings. Previous studies of women in the general population and in those with a family history of ovarian cancer have also shown that OCs reduced the risk of ovarian cancer. However, the potential risks associated with OCs should also be considered. For example, it is not known whether the pill increases breast cancer risk for women with an inherited tendency for developing this cancer. A very small study of women with a BRCA1 or BRCA2 alteration suggested that the pill may be associated with increased risks for breast cancer, but larger studies need to confirm these findings. Individuals who are not found to carry a mutation in the BRCA1 or the

BRCA2 gene, but have a family history of ovarian cancer, may still wish to consider the benefits of oral contraceptive use while also weighing the potential risks.

A Note about Hormone Replacement Therapy:

Hormone replacement therapy (HRT) provides relief from menopausal symptoms as well as health benefits such as protection from heart and bone disease (i.e., osteoporosis). However, studies have shown that long-term use of HRT, either with estrogen alone or estrogen and progesterone, somewhat increases breast cancer risk. Thus, there are concerns about the use of HRT in women at high risk for breast cancer, and in those with a prior history of breast cancer. Currently, there are other medications or interventions aside from HRT that can treat osteoporosis and lower cholesterol (one of the risk factors for heart disease). There are no data or standard recommendations regarding the use of HRT in women at high risk for breast cancer, including those who have an alteration in the BRCA1 or BRCA2 gene. Because of the potential for increased breast cancer risks, long term use of HRT, particularly for those women opting to undergo close surveillance for breast cancer, may not be desirable. However, a recent study demonstrated that healthy women with a known inherited risk for breast cancer who had their ovaries removed before age 50 still had reduced breast cancer risks even if they took HRT. In general, it is thought the amount of hormones in HRT is not more than what is produced naturally (until menopause). Therefore, high risk women may consider taking HRT after oophorectomy until age 50, after carefully weighing the risks and benefits. Your doctor can work with you or your family members to help make an informed decision about which options to consider.

Issues to Consider about Oral Contraceptives and Hormone Replacement Therapy:

As with every important medical decision, the relative pros and cons of using oral contraceptives (OCs) or hormone replacement therapy (HRT) must be weighed very carefully. We are just beginning to learn what the effects of these medications may be in women with a BRCA1 or BRCA2 alteration. It is therefore a good idea to consider a range of options with your physician that may provide benefits similar to those provided by taking OCs or HRT. For example, it is important to consider what other forms of birth control may be acceptable; what non-hormonal methods are available to reduce the symptoms of menopause; what other medications or interventions may provide similar health benefits to HRT in reducing risk of heart disease and osteoporosis. Each woman must make an informed decision with which she is comfortable.

Risk Avoidance:

All individuals, regardless of their BRCA1/BRCA2 status, are encouraged to minimize their intake of alcohol and dietary fat, refrain from tobacco smoking, and minimize sun exposure. While these measures may not reduce the risk of breast and ovarian cancer, they do have proven benefits in maintaining good general health and in reducing the risk of other cancers.

Genetic Testing: Pros and Cons

There are potential benefits to having genetic testing, as well as potential risks of testing and limitations to the information that is obtained. Each individual needs to consider whether the potential benefits outweigh the potential risks in order to make his or her own decision about whether or not to be tested. All individuals who decide to provide a blood sample for genetic testing must sign a consent form, which contains additional information about the benefits, limitations, and risks of genetic testing. Some of the major points are highlighted below.

PROS:

There are potential benefits of testing which may lead some individuals to decide to have testing for alterations in cancer susceptibility genes.

Increased knowledge: Genetic testing may provide more information about risk for getting cancer and provide insight as to why cancer developed in an individual or family.

Health care decisions: Information about cancer risk can facilitate decisions about whether certain screening tests should be considered and may help women decide about prophylactic surgery. In addition, individuals who learn that they carry an alteration in the BRCA1 or the BRCA2 gene may be able to participate in clinical trials examining the benefits of certain medical interventions and prevention strategies.

Information for other relatives: Testing may provide information about cancer risk for children, siblings, and other family members.

Emotional benefits: Learning the results of testing may produce a sense of psychological relief because uncertainty about cancer risk may be reduced.

Contribution to research: Participation in genetic counseling and testing programs will help further understanding about inherited cancer. In addition, we have also established a family registry to learn more about hereditary breast/ovarian cancer, including the risks associated with BRCA1 and BRCA2 alterations, the possible discovery of new genes, and the best way to prevent and treat hereditary cancer. You and your relatives may be invited to participate in this program. Through the registry, you and your family members would be asked some medical questions and may be offered the opportunity to contribute a blood sample for future research. You and your family members may also be invited to participate in The Cancer Genetics Network (CGN), a national multi-center project sponsored by the National Cancer Institute (NCI). The purpose of the CGN is to help researchers and health care providers understand the causes of cancer, which may lead to better methods of early detection, prevention, and treatment of cancer.

CONS:

There are limitations and potential risks of testing which may lead some individuals to decide not to have testing. In such instances, we may still ask that individuals complete a few short telephone interviews to help us learn more about reasons why people decide not to have testing.

Difficulties in test result interpretation: Because genetic testing for BRCA1 and BRCA2 alterations is investigational, it is possible that test results will be uninformative or difficult to interpret. Genetic testing does not provide a definitive answer about an individual's risk for getting cancer or getting cancer again.

Length of time to receive results: There is a possibility that test results will take several weeks to acquire. Such a delay may make it more difficult to make decisions about cancer screening and prevention, especially for women with a new diagnosis of breast cancer.

Discrimination: Genetic testing may place individuals at risk for discrimination by health, life, and disability insurers, as well as employers. Knowledge that you have a genetic predisposition to cancer may compromise your ability to obtain or maintain insurance coverage. At the present time, fewer than half of the states have laws restricting the extent to which genetic information may be used by health insurers. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer and use the answers in their underwriting decisions. However, recently enacted federal legislation may help to protect those individuals who decide to undergo genetic testing. In August 1996, President Clinton signed The Health Insurance Portability and Accountability Act of 1996 (also known as the Kennedy-Kassebaum Law), which recognizes "genetic information" as protected medical information, and forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs. The Act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to get into the plan or to stay in the plan) that is greater than that for a "similarly situated" individual enrolled in that plan. The term "similarly situated" means that a plan or coverage would be permitted to vary benefits available to different groups of employees, such as full-time vs part-time or employees in different geographic locations. A limitation of the Act is that the premiums charged for individual health insurance are not restricted by the Act, and need only comply with state law. These insurance reform provisions of the Act went into effect on July 1, 1997. The Health Insurance Portability and Accountability Act of 1996 is a major step toward gaining protection for individuals who undergo genetic testing. However, it does not address the issue of confidentiality and does not require the individual's permission to release genetic information. Although there has been no federal legislation passed regarding the areas of medical record privacy, employment, and other forms of insurance, such as life and disability, both the Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination. The staff of the CARE program will do everything possible to

protect the privacy of genetic testing results for participants in the CARE program. Each individual is identified by a unique ID number and no information about a participant of the program is released to third parties without the consent of that individual. Likewise, our research program has been issued a Certificate of Confidentiality from the Department of Health and Human Services, which allows the CARE program to withhold information about CARE participants from any outside sources, unless that individual has given written consent.

Emotional implications: Individuals who learn their test results, especially when an alteration is identified, may feel sad, angry, or anxious. For women with a new diagnosis of breast cancer who have chosen to undergo genetic testing, these feelings may be more intense. In addition, individuals may have anxiety while waiting for results prior to undergoing treatment. It is important to consider the potential impact of genetic testing on children or other relatives, as relationships may become strained and individuals may feel guilty regarding the outcome or possible outcome of testing. Each person responds differently to information about risk and in some circumstances, psychological counseling and support may be helpful.

Family information: The correct interpretation of the test results is based on the family history provided by each participant. In gathering this history and pursuing genetic testing, it is possible that an individual may learn unanticipated information, regarding adoption or non-paternity (i.e., that someone is not the biological father of a child).

Resources:

Many resources for information and support are available at Georgetown University Medical Center and in the surrounding community, as listed below:

Physicians/Professional Services at GUMC:

Other referrals to specific physicians, nutritionists, or psychologists are provided upon request. Other resources include:

Betty Lou Ourisman Center (202) 687-2122

Offers women the keystones of breast health: instruction in monthly breast self-examination, breast examinations by a health care professional, and regular mammograms.

Lombardi CancerLine (202) 784-4000

Cancer Information and Referral

An information line with a registered nurse who is certified in oncology, and who can answer questions about cancer screening, diagnosis, and treatment. She can also answer questions regarding clinical trials and make referrals within Georgetown and Lombardi Cancer Center.

Other Resources:

****** The information provided in the following resources is intended for additional educational purposes only, and is not meant to replace professional medical recommendations. In addition, the specific content of these resources (especially the web sites), has not necessarily been reviewed by our staff or by medical authorities for accuracy. Therefore, all screening, treatment and prevention information should be discussed with a health care provider.

General Information

American Cancer Society

1599 Clifton Road, NE

Atlanta, GA 30329

1-800-ACS-2345

Web site: <http://www.cancer.org>

A nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education, and service. The web site provides detailed screening procedures for several types of cancer, including breast, ovarian, prostate, and colon.

Association of Cancer Online Resources

Web site: <http://www.acor.org>

ACOR information system provides an assortment of cancer related web sites. This site also contains numerous electronic mailing lists that provide new information and support groups for those affected by cancer.

Cancer Care, Inc

275 7th Avenue

New York, NY 10001

1-800-813-HOPE (4673)

Web site: <http://www.cancercareinc.org>

A social service agency that provides professional counseling and information to women with cancer and their family members.

CancerEducation.com

Web site: <http://www.cancereducation.com>

This site provides up-to-date and accurate educational programming and information for healthcare professions, cancer patients and their families.

National Cancer Institute's Cancer Information Service

1-800-4-CANCER

Web site: <http://cancernet.nci.nih.gov>

A nationwide telephone service for cancer patients and their families, the public, and health care professionals providing up-to-date and understandable information about cancer screening, diagnosis, and treatment. Many publications are available free of charge. In addition, the web site offers access to the Physician's Data Query (PDQ), NCI's comprehensive cancer database, which contains summaries on cancer treatment, screening and prevention. It also provides a registry of cancer clinical trials from around the world, and a directory of physicians, genetic counselors and organizations that provide cancer care.

Oncolink

<http://www.oncolink.upenn.edu>

A multimedia cancer information resource developed and maintained by the University of Pennsylvania Cancer Center.

Cancer Genetics Information on the World Wide Web

<http://surgery.mc.duke.edu/purcell/cancer genetics/>

This site provides links to numerous cancer genetics web sites for several different types of cancer.

Breast Cancer Information

Breast Cancer.Net

<http://www.breastcancer.net>

Internet news items related to breast cancer are published daily and provided free of charge as part of this service. Over 2,200 breast cancer survivors, health professionals, and legislators subscribe.

For Men with Breast Cancer

http://www.y-me.org/4_men.htm

A link offered as part of the Y-Me web site, which is specifically designed for males who have been diagnosed with breast cancer.

<http://interact.withus.com/interact/mbc>

A web site designed by a male dealing with a diagnosis of breast cancer. It offers information and support for male breast cancer patients.

Colon Cancer Information

<http://www.cancer.org>

The American Cancer Society provides a comprehensive overview of colon cancer as part of their web site. Under the heading "common cancers", click on colon/rectum cancer.

Prostate Cancer Information

<http://www.ustoo.com>

UsToo is an independent network of support group chapters for men and their families dealing with a diagnosis of prostate cancer.

<http://www.cancer.org>

This site also provides a comprehensive overview of prostate cancer. Under the heading "common cancers", click on prostate cancer.

Advocacy

National Alliance of Breast Cancer Organizations (NABCO)

9 East 37th Street, 10th Floor

New York, NY 10016

1-888-80-NABCO or 1-888-806-2226

Web site: <http://www.nabco.org>

A network of breast cancer organizations that provides information, assistance, and referrals to anyone with questions about breast cancer, and acts as a voice for the interests and concerns of breast cancer survivors and women at risk.

National Breast Cancer Coalition

1707 L Street, NW
Suite 1060
Washington, DC 20036
(202) 296-7477

Web site: <http://www.natlbcc.org>

A national advocacy group concerned with furthering research about breast cancer. The group is also involved in lobbying efforts for issues such as legislation to protect against genetic discrimination.

Susan G. Komen Breast Cancer Foundation – Headquarters

5005 LBJ Freeway – Suite 370
Dallas, TX 75244
1-800-IM-AWARE

Web site: <http://www.komen.org>

An organization dedicated to the advancement of breast cancer research, education, screening and treatment. The Komen foundation is also the sponsor for the National Race for the Cure, held in several cities nationwide.

National Ovarian Cancer Coalition (NOCC)

500 NE Spanish River Blvd. Suite #14
Boca Raton, FL 33431
1-888-OVARIAN (682-7426)

Web site: <http://www.ovarian.org>

The NOCC was founded by ovarian cancer survivors whose mission it is to save women's lives by raising awareness about ovarian cancer. Their goal is to increase research opportunities and to improve treatment methods for ovarian cancer.

Ovarian Cancer National Alliance: Ovar'coming Together

PO Box 33107
Washington, DC 20033
(202) 530-2900

Web site: <http://www.ovariancancer.org/index.shtml>

The mission of the Ovarian Cancer National Alliance is to unite organizations and individuals in the fight to overcome ovarian cancer. This organization also publishes a quarterly newsletter entitled Alliance Action, which highlights advocacy efforts of ovarian survivors and provides information regarding special events

and activities for patients and their families.

Legislative Information on the Internet

<http://thomas.loc.gov/>

A service of Congress through its library

<http://college.georgetown.edu/research/ihrp/hipaa/>

A web site maintained by Georgetown University describing an individual's rights to buy and keep health insurance in each state, including information regarding the Kennedy-Kassebaum Law.

<http://members.aol.com/bclegis/index.htm>

A page provided by a breast cancer survivor designed to keep people informed of pending breast cancer legislation in the US Congress.

<http://www.sclld-nci.net/>

The National Cancer Institute (NCI) maintains the State Cancer Legislative Database (SCLD). This web site provides information regarding state legislation and regulations about cancer related topics.

Support

Conversations

This is a newsletter for individuals dealing with a diagnosis of ovarian cancer. It provides information regarding events and opportunities as well as resources for ovarian cancer patients. For further information or to receive a free subscription, please call (806) 355-2565, or visit their web site at <http://www.ovarian-news.com>.

FORCE – Facing Our Risk of Cancer Empowered

<http://www.facingourrisk.org>

FORCE is a nonprofit organization that provides information and support for women with an increased risk for developing breast and/or ovarian cancer, due to a genetic predisposition or family history of these cancers.

Gilda's Club, Inc.

195 W. Houston Street
New York, NY 10014
(212) 647-9700

Web site: <http://www.gildasclub.org>

Education and support for people with cancer and their families.

SHARE

1501 Broadway, Suite 1720
New York, NY 10036
(212) 719-0364

Hotline (English) -Breast Cancer (212) 382-2111

-Ovarian Cancer (212) 719-1204

(Spanish) – (212) 719-4454

Web site: <http://www.sharecancersupport.org>

SHARE is a self-help organization that provides information to women and their family members who have been affected and/or impacted by a diagnosis of breast and/or ovarian cancer.

Sisters Network, Inc.

8787 Woodway Drive, Suite 4207
Houston, TX 77063
(713)-781-0255

Web site: <http://www.sistersnetworkinc.org>

Local Chapter

16 Brickford Lane
Pikesville, MD 21208
(410) 486-6325

This organization provides information and support groups for African American women with breast cancer.

Y-ME National Breast Cancer Organization

212 West Van Buren Street, 4th Floor
Chicago, IL 60607-3908

1-800-221-2141 (English)

1-800-986-9505 (Spanish)

Web site: <http://y-me.org>

Books/Publications:

Breast Cancer

Please visit the following web site for additional titles:

<http://members.aol.com/healthbook/breastcancer/index.htm>

Baker, N.C. **Relative Risk: Living With a Family History of Breast Cancer.** New York: Penguin. 1992. A guide for women at risk for developing breast cancer. This book provides coping mechanisms for dealing with feelings of vulnerability and susceptibility, and offers practical advice on protecting one's health.

Berger, K., and Bostwisch, J. **A Woman's Decision. Breast Care, Treatment, and Reconstruction.** St Louis: Quality Medical Publishing, Inc. 1994. An authoritative text designed to help women assess their options, familiarize themselves with breast cancer treatment, and prepare themselves for what to expect medically and emotionally from reconstructive surgery.

Latour, K. **The Breast Cancer Companion.** New York: William Morrow & Co. 1993. Written in lay terms by a breast cancer survivor, this practical guide discusses everything a breast cancer patient needs to know from diagnosis through recovery. The text is also liberally illustrated with personal patient accounts of their experience.

Link, J. **The Breast Cancer Survival Manual: A Step-By-Step Guide for the Woman With Newly Diagnosed Breast Cancer.** New York: Henry Holt. 1998. Written by an oncologist, this comprehensive guide is designed for the newly diagnosed breast cancer patient. This book provides information to help a newly diagnosed patient make intelligent decisions regarding surgery and treatment options, at what can be an emotionally charged time.

Tarkan, L. **My Mother's Breast Cancer: Daughters Face their Mothers' Cancer.** Dallas: Taylor Publishing Company. 1999. The author profiles a wide range of women who have witnessed the effects of their mothers' breast cancer. She shares in their own words their fears, anger, guilt, and grief. The book also features information on methods of determining risk levels, genetic testing, possible preventive measures, and approaches to facing anxiety. It also offers strategies from leading psychologists and psychiatrists for coping and providing resources for women and men alike.

Ovarian Cancer

Please visit the following web site for additional titles:

<http://www-personal.umich.edu/~bethany/ovcastory.html>

Piver, M, and Eltabbakh, G. **Myths and Facts about Ovarian Cancer.** New York: PRR. 1997. Written by Dr. M. Steven Piver, the Founder and Director of the Gilda Radner Familial Ovarian Cancer Registry at Roswell Park Cancer Center, this text

offers the most current screening and treatment options for ovarian cancer. It also contains numerous illustrations and patient quotes.

Radner, Gilda. **It's Always Something.** New York: Simon and Schuster. 1989. The author's autobiography, this book describes the comedienne's career and how her diagnosis of ovarian cancer affected her life.

Prostate Cancer

Please visit the following web site for additional titles:

<http://members.aol.com/healthbook/prostatecancer/index.htm>

Garnick, M. **The Patient's Guide to Prostate Cancer.** New York: Plume. 1996. Written by a Harvard Medical School professor, this book provides information and emotional support to men who have been diagnosed with prostate cancer.

Oesterling, J., and Moyad, M. **The ABC's of Prostate Cancer: The Book That Could Save Your Life.** Lanham: Madison Books. 1997. This book explains the facts that men need to know about prostate cancer. In addition, it contains personal accounts of more than 50 well-known survivors of prostate cancer, including Bob Dole.

Colon Cancer

Please visit the following web site for additional titles:

<http://www3.cancer.org/cancerinfo>

Levin, B. **Colorectal Cancer: A Thorough and Compassionate Resource for Patients and their Families.** New York: Villard Books. 1999. This book provides information and support to individuals and their families dealing with a colon cancer diagnosis.

Miskovitz, P. **What to Do If You Get Colon Cancer: A Specialist Helps You Take Charge and Make Informed Choices.** New York: John Wiley & Sons. 1997. Written by Dr. Paul Miskovitz, this encouraging and authoritative guide provides information regarding colon polyps and colon cancer. It also provides advice on how to cope with the physical and emotional effects of a colon cancer diagnosis.

Genetic Testing

Genetic Testing for Breast Cancer Risk: It's Your Choice. A free booklet from the National Cancer Institute, which provides a general overview on testing for breast and ovarian cancer risk. This information is also available in video format.

Understanding Genetic Testing. A free booklet by the National Cancer Institute providing information about gene testing. This booklet also provides answers to frequently asked questions about the potential risks and benefits of genetic testing.

Clinical Trials

Taking Part in Clinical Trials: Cancer Prevention Studies. What Participants Need to Know. A free publication from the National Cancer Institute, this booklet is for individuals who would like more information concerning cancer prevention clinical trials.

Family Concerns/Support

Harpham, W.S. **When a Parent has Cancer: A Guide to Caring for Your Children.** New York: Harper Collins. 1997. Written by an internist who herself has battled cancer, this informative text explains how to prevent and respond to common problems experienced by children whose parent has been diagnosed with cancer.

Taking Time. Support For People With Cancer and the People Who Care About Them. Another free publication from the National Cancer Institute, this booklet provides support for the cancer patient and their family.

General Publications

Krause, C. **How Healthy is Your Family Tree? A Complete Guide to Tracing Your Family's Medical and Behavioral History.** New York: Simon and Schuster. 1995. A helpful guide to gaining vital information about your family history.

McGinn, K., and Haylock, P. **Women's Cancers: How to Prevent Them, How to Treat Them, How to Beat Them.** California: Hunter House. 1998. Written by two nurses in textbook format, this resource is designed to help women diagnosed with or at risk for several types of cancer, including breast and ovarian.

What You Need to Know Series: Breast, Ovarian, Colon, Prostate and Other Cancers. Free publications from the National Cancer Institute's Cancer Information Service explaining the symptoms, diagnosis, and treatment of these cancers. Please contact 1-800-4-Cancer for more information on how to obtain these publications.

Local Chapter - Y-ME of the National Capital Area

6000 Stevenson Avenue, Suite 203

Alexandria, VA 22304

Web site: <http://www.y-menca.org/>

(703) 461-9595 or 96

Outside of VA - 1-800-970-4411

Y-ME is a comprehensive breast cancer support program founded in 1978 by two breast cancer patients. It provides a national support hotline for breast cancer survivors. In addition, their web site provides a link to a listing of resources for breast cancer survivors and their families.

GEORGETOWN

The Art of Medicine



A Comprehensive Cancer
Center Designated by the
National Cancer Institute

outcomes. Answers to questions in molecular genetics and genetic epidemiology that will have important implications for clinicians can be expected. The process of genetic counselling will have to be continuously refined and supplemented so that the benefits of genetic testing for women can be increased while the potential for harm is reduced.

Beth N Peshkin, *Caryn Lerman

Cancer Genetics, Georgetown University Medical Center, Washington, DC 20007, USA

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- 3 Watson M, Lloyd SM, Eeles R, et al. Psychosocial impact of testing (by linkage) for the *BRCA1* breast cancer gene: an investigation of two families in the research setting. *Psycho-Oncol* 1996; 5: 233-39.
- 4 Patenaude AF, Schneider KA, Kieffer SA, et al. Acceptance of invitations for p53 and *BRCA1* predisposition testing: factors influencing potential utilization of cancer genetic testing. *Psycho-Oncol* 1996; 5: 241-50.
- 5 Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer* 1999; 79: 868-74.
- 6 Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. Psychological responses to *BRCA1* mutation testing: preliminary findings. *Health Psychol* 1997; 16: 63-72.
- 7 Lerman C, Hughes C, Lemon SJ, et al. What you don't know can hurt you: adverse psychological effects in members of *BRCA1*-linked and *BRCA2*-linked families who decline genetic testing. *J Clin Oncol* 1998; 16: 1650-54.
- 8 Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer—II: *BRCA1* and *BRCA2*. *JAMA* 1997; 277: 997-1003.
- 9 Parmigiani G, Berry DA, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. *Am J Hum Genet* 1998; 62: 145-58.
- 10 Cull A, Miller H, Porterfield T, et al. The use of videotaped information in cancer genetic counselling: a randomized evaluation study. *Br J Cancer* 1998; 77: 830-37.

Physical activity and knee osteoarthritis

Knee osteoarthritis is a major cause of pain and disability in older people, and accounts for some 9000 knee arthroplasties carried out annually in England and Wales.¹ Although there are many pathophysiological mechanisms that may culminate in "joint failure", the main determinants of knee osteoarthritis are thought to be constitutional predisposition to the disorder at several joint sites, combined with local biomechanical stress. Established risk factors include older age, female sex, evidence of osteoarthritis at other joint sites, obesity, and previous injury or surgery to the knee. Evidence is accumulating that certain physical activities at work and during leisure also increase the risk of knee osteoarthritis.

Studies relating occupational physical activity to the risk of knee osteoarthritis fall into two broad categories: those that have contrasted the prevalence of the disorder among groups of workers exposed to generally high levels of physical loading of the joint with others in sedentary occupations, and those that focus on specific activities done in the workplace.² Thus, case-control studies have shown that shipyard workers, miners, dockers, and carpet or floor layers have significantly greater frequencies of knee osteoarthritis than control groups of clerical workers or people doing light manual work. These data have been supplemented by population-based case-control and cohort studies showing that jobs that entail frequent and long durations of kneeling or squatting are also associated

with a two-fold to three-fold increase in the risk of knee osteoarthritis. A systematic overview of this evidence³ suggested that the relation between occupational kneeling and knee osteoarthritis among men was robust and consistent, with a summary relative risk of about 2.0 associated with such occupational exposures.

The relation between knee osteoarthritis and physical activity during leisure time is more controversial.⁴ The evidence is best categorised according to the type of physical activity (low or high impact) and the underlying health of the exposed joint. Epidemiological studies of low-impact activity in normal joints (for example, recreational jogging) suggest no increase in the risk of self-reported knee-joint pain or radiographic evidence of osteoarthritis. By contrast, high-intensity and high-impact physical activity are associated with a definite, if small, increase in the risk of the disorder. Thus, a UK study of ex-elite long-distance runners and tennis players found a two-fold to a three-fold increase in risk of radiological osteoarthritis at the knees and hips.⁵ Another found that the prevalence of radiographic knee osteoarthritis was 4.2% in non-elite former soccer players and 15.5% in elite former players, compared with only 1.6% in controls.⁶ Soft-tissue injuries of the knee (a known risk factor for later osteoarthritis) are frequently associated with participation in such high-impact sports. However, the data suggest independent effects of high-impact loading and injury in causing knee osteoarthritis. A study of 77 soccer players, 20-30 years after knee-joint injuries and partial meniscectomy, showed that 25% of those with an intact anterior cruciate ligament had knee osteoarthritis, compared with 71% of those who had sustained a rupture of this ligament.⁷ Features of knee osteoarthritis arose 10-20 years after meniscal or cruciate-ligament injury.

A recently published analysis from the Framingham Osteoarthritis Study supports the previously observed associations between heavy physical activity and the development of knee osteoarthritis in later life.⁸ This study adds two important dimensions to the understanding of the relation. First, the inclusion of baseline and follow-up knee radiographs in this cohort permitted demonstration of the relation between activity levels and incident radiographic knee osteoarthritis. These data suggest that mechanical risk factors for knee osteoarthritis (most notably knee injury, obesity, and physical activity) are more important determinants of initiation than of progression. Second, the Framingham data suggest that the effect of heavy physical activity is strongest among obese individuals.

What implications do these observations have for the prevention of knee osteoarthritis and the management of patients with established disease? The association between certain occupational physical activities and the risk of knee osteoarthritis in men is consistent, and consideration should be given to preventive measures in jobs that involve occupational kneeling or squatting. Work for long times in such postures should, if possible, be avoided; knee pads are already recommended for protection against prepatellar bursitis, but may also reduce the risk of later patellofemoral osteoarthritis. Non-occupational risk factors that interact with those in the workplace (for example, obesity) should be controlled. Finally, the data provide support for the compensation of knee osteoarthritis as an occupational disorder among people who kneel or squat for long periods in their work. The association between leisure physical activity and knee

- 2 The management of menorrhagia. *Effective Health Care* Leeds: University of Leeds 1995; 9: 1-14.
- 3 Aberdeen Endometrial Ablation Trials Group. A randomised trial of endometrial ablation versus hysterectomy for the treatment of dysfunctional uterine bleeding: outcome at four years. *Br J Obstet Gynaecol* 1999; 106: 360-66.
- 4 Higham JM. Clinical associations with objective menstrual blood volume. *Eur J Obstet Gynaecol Repro Biol* 1999; 82: 73-76.
- 5 Lilford RJ. Hysterectomy: will it pay the bills in 2007? *BMJ* 1997; 314: 160.
- 6 Guideline Development Group. The initial management of menorrhagia: evidence-based clinical guidelines no 1. London: Royal College of Obstetricians and Gynaecology, October 1998.
- 7 Crosignani PS, Vercellini P, Mosconi P, et al. Levonorgestrel releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional bleeding. *Obstet Gynaecol* 1997; 90: 257-63.
- 8 Irvine GA. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for idiopathic menorrhagia. *Br J Obstet Gynaecol* 1998; 105: 592-98.
- 9 Killesten N, Istre O. A randomised study comparing levonorgestrel intrauterine system (LNGIUS) and transcervical resection of the endometrium in the treatment of menorrhagia: preliminary results. *Gynecol Endosc* 1998; 7: 61-65.
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- 11 Garry R. Endometrial ablation and resection: validation of a new surgical concept. *Br J Obstet Gynaecol* 1997; 104: 1329-31.
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Genetic counselling for hereditary breast cancer

Although initial interest in gene testing seemed to be substantial,¹ studies in high-risk families have shown that the uptake is below 50%. The largest of these studies revealed that of 279 individuals from 13 families, only 43% decided to receive *BRCA1* test results.² This finding was similar to the 41% uptake rate noted in two families participating in *BRCA1* linkage studies.³ However, another small study found that 80% of 29 members of two *BRCA1* families accepted genetic testing.⁴ Factors that may influence decisions include the strength of the family history, the perception of the benefits of testing, and the estimation of risk of being a gene carrier.⁵

In a report highlighting some of the challenges associated with genetic counselling for women at increased risk of breast cancer, M Watson and colleagues emphasise that a woman's perception of this risk may influence both her attitude to screening and her psychological well-being.⁶ The increasing availability of genetic testing should offer opportunities to improve assessment of this risk and how it is imparted to patients.

Women who seek genetic counselling and testing may represent a psychologically vulnerable group in that they may exhibit more cancer-specific distress or mood disturbances.^{1,5} Although test-related distress may increase immediately after results are disclosed,⁶ early data from high-risk families have shown no significant increases in global distress or anxiety among mutation carriers.² However, once a *BRCA1* or *BRCA2* mutation has been found, family members who are distressed about their risk, yet decline testing, may be more likely than those tested to experience adverse psychological effects, irrespective of whether the test results were positive or negative.⁷ Because families in these research studies were highly selected, the findings may not apply to clinic-based populations, in which family experience with cancer may

Research issues in genetic counselling for hereditary breast cancer

Validation of probability models for mutation detection
Correlations between genotype and phenotype (clinical outcome)
Role of genetic and other risk factors that modify penetrance
Efficacy of early detection and prevention strategies
Cost-effectiveness of genetic counselling and testing
Long-term impact of testing on emotional well-being and medical decisions
Optimum methods of genetic counselling and presentation of risk information
Adjunctive methods of education and psychological counselling

be more limited and for whom the service provided may be less extensive.

Most women with no history of breast or ovarian cancer who test positive for a *BRCA* mutation do not intend to have prophylactic surgery, at least in the short-term.² Thus, reinforcement of conventional screening and other risk-reduction options is important.⁸ Initial anxiety about the potential risk of cancer⁶ may prevent women from seeking early detection, thus genetic counselling may need to be followed by psychological interventions.

Informed consent for women considering genetic testing must include not only the benefits and risks of testing but also the uncertainties of risk assessment and medical decision-making. Models to estimate an individual woman's probability of carrying a *BRCA1* or *BRCA2* mutation are being developed⁹ (panel) and, in view of the expense of testing and the possibility of uninformative results, such estimates may be useful. In addition, cancer-risk estimates may be tailored on the basis of the specific mutation identified, the impact of potential modifier genes such as *CYP1A1* and *HRAS1*, and gene-environment interactions (eg, reproductive factors and hormone use). Long-term outcome data will also become available for the assessment of the efficacy of screening and prevention options. Also, whether tamoxifen reduces breast-cancer risk in *BRCA1* or *BRCA2* carriers and what level of risk reduction is conferred by prophylactic surgery are not known. Such information is critical to informed decision-making.

The best way of obtaining informed consent and providing genetic counselling is also being explored. Several studies, including that by Watson and colleagues,⁶ show that women find it difficult to retain the quantitative risks provided during genetic counselling, so other ways of delivering this information need to be investigated. Also needed is information on whether comprehension, compliance with screening guidelines, and psychological adjustment can be improved by expansion of the genetic-counselling sessions. Videotapes and interactive computer programs¹⁰ may be useful adjuncts, for example; tools to identify individuals most likely to experience adverse effects from genetic testing and those who might benefit from the addition of psychosocial interventions would also be useful.

Some women, especially those from high-risk families, have already chosen to undergo genetic testing for hereditary breast cancer despite the many uncertainties. Experience from carefully monitored research protocols is providing important information about who wants this test and how test results affect medical and psychosocial

Spiritual Faith and Genetic Testing Decisions among High-Risk Breast Cancer Probands¹

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Abstract

Despite widespread access to genetic testing for the *BRCA1* and *BRCA2* breast cancer susceptibility genes, little is known about rates or predictors of test use among individuals from newly ascertained high-risk families who have self-referred for genetic counseling/testing. The objective of this study was to examine rates of test use within this population. In addition, we sought to determine whether spiritual faith and psychological factors influenced testing decisions. Participants were 290 women with familial breast cancer. All were offered genetic counseling and testing for alterations in the *BRCA1* and *BRCA2* genes. Baseline levels of spiritual faith, cancer-specific distress, perceived risk, and demographic factors were examined to identify independent predictors of whether participants received versus declined testing. The final logistic model revealed statistically significant main effects for spiritual faith [odds ratio (OR), 0.2; 95% confidence intervals (CIs), 0.1 and 0.5] and perceived ovarian cancer risk (OR, 2.4; 95% CIs, 1.3 and 4.7) and a statistically significant spiritual faith by perceived risk interaction effect. Among women who perceived themselves to be at low risk of developing breast cancer again, those with higher levels of spiritual faith were significantly less likely to be tested, compared with those with lower levels of faith (OR, 0.2; 95% CIs, 0.1 and 0.5). However, among women with high levels of perceived risk, rates of test use were high, regardless of levels of spiritual faith (OR, 1.2; 95% CIs, 0.4 and 3.0). These results highlight the role that spirituality may play in the decision-making process about genetic testing.

Introduction

The *BRCA1* and *BRCA2* genes are believed to account for most HBC³ cases (1). Among women affected with breast cancer, inherited mutations in *BRCA1* or *BRCA2* are associated with a significantly increased risk of developing new primary cancers (2-4). Preliminary reports suggest that 40-80% of HBC family members elect to learn their genetic status for *BRCA1/2* (5, 6), with somewhat higher rates among persons with cancer as compared with those who are unaffected (5). However, these reports were based on a few large HBC families, most of whom were members of hereditary cancer registries and participants in prior genetics research. These participants may not be representative of newly ascertained individuals who self-refer for genetic counseling (5). In the present study, we evaluated *BRCA1/2* test use among women who had self-referred to a free genetic counseling/testing research program. The study focused on women who were affected with breast cancer, because standard clinical practice is to first screen for mutations among a likely carrier in the family before proceeding to unaffected relatives.

A novel goal of this study was to explore the role of spirituality in testing decisions. Although spirituality has been linked to the avoidance of health risk behaviors (7) and decreased mortality for a variety of diseases (8), little is known about its effects on medical decision making or on genetic testing, in particular. However, research and theory on coping with illness suggests that spirituality may actually deter participation in genetic testing for cancer risk. For example, research has shown that highly spiritual individuals are more optimistic (7), have greater acceptance of their cancer diagnoses (9), and are more likely to attribute health threats to external forces than to factors such as heredity (10). Thus, a woman with breast cancer who is highly spiritual may question the need for genetic testing because she accepts her condition and believes that whether she becomes ill or not is out of her hands. This is consistent with a previous study showing an inverse relationship between spirituality and interest in prenatal testing (11). Therefore, we hypothesized that highly spiritual individuals would be less likely than less spiritual individuals to receive *BRCA1/2* testing.

The present study also focused on cancer-specific distress and perceived risk, two psychological variables that have been implicated in *BRCA1/2* testing decisions. Perceived risk and cancer-specific distress have predicted intentions to obtain *BRCA1/2* testing (12). For example, among women from HBC families, we found that cancer-specific distress predicted *BRCA1/2* test use (13). Similarly, in a recent study, both perceived risk and cancer worries were associated with genetic testing for colorectal cancer susceptibility (14). Therefore, in

Received 10/7/99; revised 1/10/00; accepted 1/28/00.

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¹ Supported by Department of Defense Grant DAMB 17-96-C-6069 (to C. L.), Grant RO1 CA/HG74861 (to C. L.) from the National Cancer Institute and Institute for Human Genome Research, and National Cancer Institute Grant KO7 CA65597 (to M. D. S.).

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³ The abbreviations used are: HBC, hereditary breast cancer; CARE, Cancer Assessment and Risk Evaluation; OR, odds ratio; CI, confidence interval.

the present study, we predicted that perceived risk and cancer-specific distress would increase the likelihood of *BRCA1/2* testing, whereas spirituality would reduce test use.

Materials and Methods

Participants. Participants were 290 adult breast cancer patients (probands) who had self-referred to the CARE program at the Lombardi Cancer Center. To be eligible, participants were required to have a family history of breast/ovarian cancer that resulted in a minimum 20% prior probability of having a *BRCA1/2* mutation (15). If a risk-conferring mutation was identified in the proband, then enrollment in the CARE program was extended to other family members. However, the present report is limited to the first 290 probands to enter CARE.

Procedures. Probands who contacted the CARE program were screened by telephone to determine eligibility. Eligible probands completed a structured telephone interview that assessed sociodemographics, cancer family history, spirituality, perceived risk, and psychological distress. Following this interview, participants were invited to a pretest education session with a genetic counselor. Information provided to probands during this 1.5–2-h session included qualitative risk assessments based on their personal and family history, details about the process of testing for *BRCA1/2* mutations and interpretation of test results, cancer risks associated with *BRCA1/2* mutations, options for cancer prevention and surveillance (based on published guidelines; Ref. 16), details about the benefits and risks/limitations of testing, and details about the possible psychosocial impact of testing.

Following the educational session, participants were offered the opportunity to provide a blood sample for *BRCA1/2* mutation testing after providing written consent. When a participant's test result became available, the participant was invited to a disclosure/counseling session. Participants could decline to continue at any point in the process (*i.e.*, before education, after education, or before the receipt of test results). Thus, uptake was defined as the actual receipt of *BRCA1/2* test results.

Measures

Predictor Variables. All predictor variables were assessed at baseline (*i.e.*, before the education session and the offer of *BRCA1/2* testing).

Sociodemographics. We assessed age, race, religion, education, and marital status.

Family History of Cancer. We assessed the number of first-degree relatives (*i.e.*, parents, siblings, children) who were affected with breast and/or ovarian cancer. We dichotomized family history as one to two affected relatives *versus* three or more affected relatives.

Spirituality. Spirituality was assessed with the following item adopted by the NIH Cancer Genetics Studies Consortium: "How strong would you say your religious or spiritual faith is?" Participants responded using a four-point Likert scale ranging from not very strong to very strong. To create groups of as close to equal in size as possible, we dichotomized this item into very strong ($n = 123$) *versus* not very strong/a little strong/moderately strong ($n = 167$).

Cancer-specific Distress. We used The Intrusion Subscale of the Impact of Events Scale (17) to measure the frequency and severity of intrusive thoughts, worries, and feelings about being at increased risk for breast and ovarian cancer. Responses were

Table 1 Demographic, psychosocial, and cancer history characteristics of the study sample

Variable	Levels	Number
Age	<45	91 (31%)
	≥45	199 (69%)
Marital status	Married	212 (73%)
	Unmarried	78 (27%)
Race	Caucasian	276 (95%)
	African American	14 (5%)
Education	<College graduate	74 (26%)
	≥College graduate	216 (74%)
Religion	Catholic	72 (25%)
	Jewish	97 (33%)
	Protestant	91 (31%)
	Other	30 (10%)
Spiritual faith	Not strong/a little strong/moderately strong	167 (58%)
	Very strong	123 (42%)
Relatives affected with breast and/or ovarian cancer	1–2	239 (82%)
	3+	51 (18%)
Perceived risk for breast cancer	Low	139 (48%)
	High	151 (52%)
Perceived risk for ovarian cancer	Low	142 (49%)
	High	148 (51%)

on a Likert scale ranging from not at all to often. The seven-item Intrusion subscale had good internal consistency (Cronbach's α , 0.84) and has been used in previous studies to measure cancer-specific distress (13, 18).

Breast Cancer Perceived Risk. We measured perceived risk for breast cancer with the following Likert-style item (19): "In your opinion, compared to other women your age, what are your chances of developing breast cancer again?" (1 = much lower to 5 = much higher). Because responses to this item were not normally distributed, we dichotomized the item as close to the median as possible [much higher ($n = 151$) *versus* somewhat higher/the same/lower ($n = 139$)].

Ovarian Cancer Perceived Risk. We measured perceived risk for ovarian cancer with the following Likert-style item: "In your opinion, compared to other women your age, what are your chances of developing ovarian cancer?" (1 = much lower to 5 = much higher). We dichotomized this item as close to the median as possible [much higher/somewhat higher ($n = 148$) *versus* the same/lower ($n = 142$)].

Dependent Variable. We classified test uptake based on whether or not participants underwent testing and received their result *versus* declined testing or test results (*i.e.*, declined to attend the pretest education session, declined to provide a DNA sample, or declined to learn their test result).

Results

Sample Characteristics. Sample characteristics are shown in Table 1. The majority of participants were Caucasian, 45 yr of age and older, married, and had a college education. Forty-two percent of participants reported that their spiritual faith was very strong. 52% reported that their risk for developing breast cancer was much higher than an average woman of the same age, and 51% reported that their risk for ovarian cancer was somewhat or much higher than an average woman of the same age.

Table 2 Bivariate associations of sociodemographic variables with *BRCA1/BRCA2* test use

Variable	Levels	% receiving test results	χ^2
Age	<45	82	0.01
	≥45	82	
Marital status	Married	82	0.00
	Unmarried	82	
Race	Caucasian	83	1.13
	African American	71	
Education	<College graduate	77	1.72
	≥College graduate	84	
Religion	Catholic	79	2.39
	Jewish	87	
	Protestant	81	
Spiritual faith	Other	77	6.01 ^a
	Not strong/moderately strong	87	
	Very strong	76	0.00
Affected relatives	1-2	82	
	3+	82	3.47 ^b
Perceived risk—breast cancer	Low	78	
	High	86	8.53 ^c
Perceived risk—ovarian cancer	Low	75	
	High	89	

^a $P < 0.05$.^b $P = 0.06$.^c $P < 0.01$.

BRCA1/2 Uptake. Of the 290 probands, 82% ($n = 238$) were tested and received results and 18% ($n = 52$) declined testing/results. Of those who declined testing/results, 73% ($n = 38$) declined preliminary education; 15% ($n = 8$) participated in the education session, but declined to provide DNA; and 12% ($n = 6$) provided DNA, but declined subsequently to learn their test result. None of the predictor variables were associated with the stage at which the decision to decline testing/results was made (*i.e.*, before education *versus* after education).

Predictors of Test Use. As shown in Table 2, spiritual faith [χ^2 (1, $n = 290$) = 6.01, $P = 0.01$] and perceived risk for ovarian cancer [χ^2 (1, $n = 290$) = 8.53, $P < 0.01$] were significantly associated with uptake. The association between breast cancer perceived risk and uptake approached significance [χ^2 (1, $n = 290$) = 3.47, $P = 0.06$] and was included in the multivariate modeling.

To identify independent predictors of receipt of *BRCA1/2* test results, we conducted a backwards stepwise logistic regression. All variables with significant bivariate associations with receipt of test results were included in the initial model (spiritual faith, breast cancer perceived risk, and ovarian cancer perceived risk). The spirituality by breast cancer perceived risk and spirituality by ovarian cancer perceived risk interactions were included in the model for exploratory purposes. On Step 1, the spirituality by ovarian cancer perceived risk interaction term was removed from the model [χ^2 change (1, $n = 290$) = 0.14, $P > 0.20$]. None of the remaining variables could be removed from the model. Thus, the final model (see Table 3) included spirituality, ovarian cancer perceived risk, breast cancer perceived risk, and the breast cancer perceived risk by spirituality interaction.

The final ORs revealed that highly spiritual women were 80% less likely to receive test results compared with less spiritual women. Compared with women with low levels of perceived risk for ovarian cancer, those with high perceived risk were about twice as likely to receive *BRCA1/2* test results.

Table 3 Logistic model predicting *BRCA1/2* test uptake

Variables in final model	OR	95% CI	P
Spirituality			
Low (referent)	1.0		
High	0.2	0.1, 0.5	0.001
Perceived risk for ovarian cancer			
Low (referent)	1.0		
High	2.4	1.3, 4.7	0.009
Perceived risk for breast cancer			
Low (referent)	1.0		
High	0.6	0.2, 1.6	0.31
Spirituality × breast cancer perceived risk			0.01
Low perceived risk			
Low spirituality (referent)	1.0		
High spirituality	0.2	0.1, 0.5	0.01
High perceived risk			
Low spirituality (referent)	1.0		
High spirituality	1.2	0.4, 3.0	0.76
Variables not in final model ^a			
Spirituality × ovarian cancer perceived risk			0.72

^a Final model: χ^2 (df = 4, $n = 290$) = 23.5, $P = 0.0001$.

The statistically significant ($P < 0.01$) spirituality by breast cancer perceived risk interaction (see Fig. 1) revealed that among women with high perceived risk for breast cancer, spirituality was unrelated to receipt of test results (OR, 1.2; 95% CIs, 0.4 and 3.0); however, among women with low perceived risk, those with high spirituality were 80% less likely to receive test results (OR, 0.2; 95% CIs, 0.1 and 0.5).

Discussion

Although *BRCA1/2* test use has been evaluated among research registry participants (5), this study is the first to examine test use among newly ascertained high-risk breast cancer probands. Overall, our 82% uptake rate was higher than the rates reported in previous studies (5, 6). This is not surprising because all participants had self-referred to a genetic counseling clinical research program and presumably were more highly motivated to have testing. This higher rate of testing probably reflects what can be expected among initial probands in clinical genetic testing programs. Not surprisingly, the majority of participants who declined testing/results declined to attend the initial education session. These individuals may have decided against testing before the baseline interview or based on the minimal information about the testing process provided at the conclusion of the baseline interview. In contrast, individuals who declined to provide a blood sample after the initial education session may have been dissuaded by the information received during the preliminary education session. Individuals who provided DNA but declined to learn the results of their gene test may have been having some difficulty deciding whether or not to receive test results.

Women who perceived their risk for ovarian cancer to be high, were most likely to be tested. This is not surprising because none of these women had previously been diagnosed with ovarian cancer. For this group, the results of a *BRCA1/2* test could have important implications for decision-making regarding ovarian cancer prevention and surveillance. Thus, women who believe that they are at high risk for ovarian cancer may be particularly motivated to learn their *BRCA1/2* status.

Although the role of spirituality in health and well-being has received extensive attention (20–22), the present

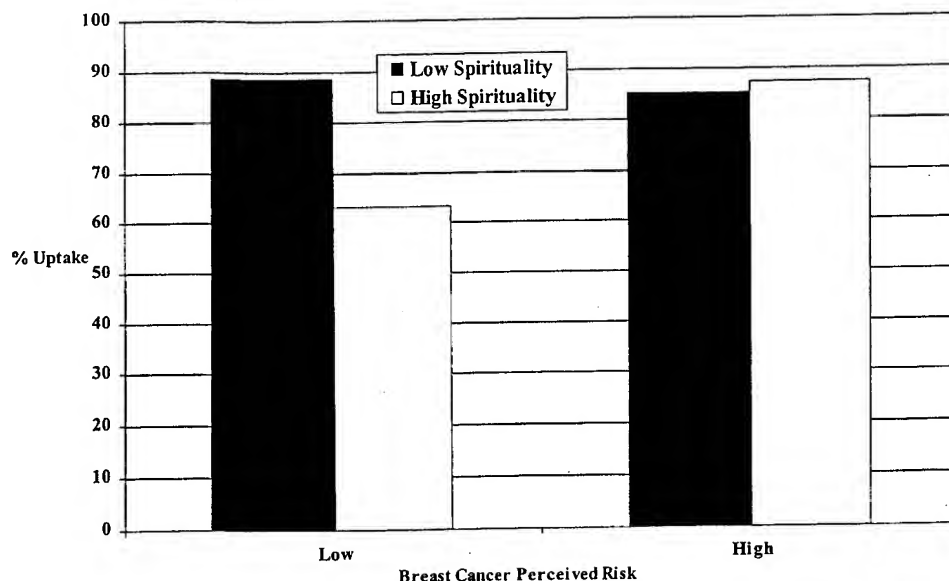


Fig. 1. The impact of perceived risk and spirituality on *BRCA1/2* test uptake.

study is the first to evaluate its influence on genetic testing for cancer susceptibility. The influence of spirituality on testing decisions may be attributable, in part, to the fact that this sample was comprised of individuals who had been previously affected with breast cancer. Previous research has found that spiritual and religious beliefs are used by cancer patients to find meaning in and to facilitate acceptance of their cancer experience (9). Whereas finding meaning may involve attempts to understand the cause of the disease, acceptance involves coming to terms with the fact that it has happened (23, 24). Breast cancer patients with higher levels of spiritual faith may be less likely to receive *BRCA1/2* testing because they are less motivated to understand the cause of their cancer and have greater acceptance.

This effect of spiritual faith on testing decisions was dependent on a woman's perceived risk of developing cancer again. Among women with low levels of perceived risk, those who were highly spiritual were five times less likely to receive test results compared with women with lower levels of spiritual faith. Importantly, spiritual faith did not predict uptake of testing among women who perceived their cancer risk to be high. The modifying influence of perceived cancer risk is consistent with previous research showing that low levels of perceived cancer risk are associated with decreased readiness and interest in genetic testing (25, 26). Thus, women with high spiritual faith and low perceived risk would be least likely to obtain *BRCA1/2* test results. However, as perceived cancer risk increases, motivation to reduce uncertainty may also increase, so that even highly spiritual women overcome their reluctance to obtain test results.

There are a few caveats about these findings. First, this sample was limited to women who self-referred for genetic counseling and agreed to complete a baseline telephone interview. Thus, the 83% uptake rate may be higher than rates of test use in population-based or clinic-based samples in which the denominator includes all eligible women. Second, all study participants were affected with breast cancer and members of high-risk families. Thus, we cannot assume that rates of test use or predictors of use would apply to low risk or unaffected individuals. Third, all testing and counseling was offered free of charge and, therefore, may overestimate levels of uptake in

fee-for-service settings. Finally, our measure of spirituality was based on a single item. The use of more sophisticated measures of spirituality could yield a better understanding of the association between spirituality and *BRCA1/2* test use. Nonetheless, the primary finding regarding the role of spirituality in testing decisions is not likely to be influenced by factors such as the cost of testing; however, this may vary among members of different ethnic groups.

Despite these limitations, this study is the first to show that high levels of spiritual faith may deter genetic testing among some women with familial breast cancer. Future research should extend these findings by evaluating the role of spirituality in the testing decisions of unaffected individuals and members of different ethnic groups. Also, additional studies are needed to elucidate the cognitive and emotional correlates of spirituality that may deter genetic testing. Such research is important to better inform clinicians about how and when to incorporate discussions of spirituality into genetic counseling.

Acknowledgments

We thank our counselors, Tiffani DeMarco and Barbara Brogan; our data managers, Kristen Willard and Rachel Manasan; and our telephone interviewers, Jerrianna Stead, Annalisa Dialino, and Lisa Smith.

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Running head: COPING AND DISTRESS AMONG GENETIC TESTING PARTICIPANTS

BRIEF REPORT

Effects of Coping Style and Test Result on Anxiety Among Women Participating in Genetic Counseling and Testing for Breast/Ovarian Cancer Risk

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This research was supported by grants DAMD 17-96-C-6069 from the U.S. Department of Defense and HG01846 from the National Human Genome Research Institute (to C. L.). Preparation of this manuscript was supported by grant CA79138 from the National Cancer Institute (to K. T.).

The authors would like to thank counselors Barbara Brogan and Tiffani DeMarco, as well as the participants in this research.

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Abstract

Using the monitoring process model (MPM), the authors examined the immediate effects of coping style and test result on the psychological distress of women at increased risk for breast/ovarian cancer. Cases selected for analysis were 107 probands and relatives of positive probands participating in genetic counseling and testing for heritable cancer risk. Specifically, we explored the relationships among coping style (high and low monitoring), test result (BRCA1/2 mutation carrier and noncarrier status), and psychological distress (state anxiety). Consistent with the MPM, higher monitoring was associated with greater psychological distress while anticipating genetic test results. After test results were disclosed, greater distress was associated with testing positive for a mutation. The implications of the findings for breast/ovarian cancer patients are discussed.

Key words: coping style, anxiety, monitoring, genetic counseling, genetic testing

Effects of Coping Style and Test Result on Anxiety Among Women Participating in Genetic Counseling and Testing for Breast/Ovarian Cancer Risk

Cancer genetic testing carries the potential to generate psychological distress among some participants. This distress may take the form of worry, intrusive ideation, dysphoric mood, or other negative emotional reactions consistent with health crises (Lerman & Croyle, 1994). To date, most research has shown that if such distress does occur, it likely happens close in time to specific testing-related episodes, such as when genetic counseling services are initially sought (Audrain et al., 1997) or during the period of time while awaiting test results (Lodder et al., 1999). Within a week after disclosing BRCA1 test results to high risk participants, one study showed carriers reporting heightened distress compared to noncarriers (Croyle et al., 1997), though their anxiety was not at clinically significant levels. A different group of researchers also studying high risk participants found no evidence of increased distress among BRCA1 carriers compared to noncarriers within one month of disclosure, though there were significant reductions in distress among noncarriers (Lerman et al., 1996). These data underscore the point that not all participants experience similar levels of genetic testing distress (Botkin et al., 1996) and also emphasize the importance of attending to key individual parameters throughout the testing process to fully understand its outcomes.

Distress among persons involved in cancer genetic counseling and testing has been found to be influenced by a number of demographic, medical, and psychological variables. These variables include mutation status, gender, and personal illness history (Croyle et al., 1997; Lerman et al., 1996), premorbid emotional functioning and social support (Smith, West, Croyle, & Botkin, 1999), anticipated emotional reaction or problems after testing (Dorval et al., 2000; Lodder et al., 1999), and coping style (Audrain et al., 1997; Houfek, Atwood, Schaefer, &

Reiser, 2000). Among the aforementioned variables, coping style may be particularly useful in discerning those participants who are most likely to experience heightened distress. That is because when faced with a health threat, persons who vigilantly attend to threatening cues (i.e., "high monitors") are more likely to report heightened distress than are persons who tend to distract themselves in the face of such information (i.e., "low monitors") (Miller, 1987).

Toward this end, Miller and colleagues developed the Monitoring Process Model (MPM) to understand the coping processes of high and low monitors facing health threats (Miller, Roussi, Caputo, & Kruus, 1995). Within this model, it is expected that high and low monitors differ in the manner in which such information is cognitively processed and interpreted. Specifically, persons high on the monitoring dimension are more likely to focus on both internal and external threat-relevant cues of pertinent stimuli and persevere on negative outcomes, thereby generating distress.

The MPM has been used to explore distress among women at risk for ovarian cancer, showing that high monitoring was associated with increased cancer risk perceptions, intrusive ideation, and general psychological distress (Schwartz, Lerman, Miller, Daly, & Masny, 1995). The MPM has also been applied to the study of persons facing long-term health threats (i.e., human papillomavirus and HIV) and supported the premise that high monitors have more disease-specific intrusive thoughts which are difficult to control (Miller, Rodoletz, Schroeder, Mangan, & Sedlacek, 1996). Other work suggests that high information-seeking individuals may be particularly distressed following cancer screening (Wardle, 1995; Wardle et al., 1993) and experience greater mood disturbances (e.g., heightened anxiety and depression) surrounding some forms of genetic testing (Phipps & Zinn, 1986; van Zuuren, 1993).

Guided by the MPM, we made several predictions about the effects of coping style on changes in anxiety during two time periods in BRCA1 and BRCA2 (BRCA1/2) genetic testing for breast/ovarian cancer risk; (1) while anticipating results and (2) immediately following results disclosure. With regard to the period of time while anticipating test results (i.e., after providing a blood sample, but before test result disclosure), we hypothesized that high monitors would experience significantly greater increases in their anxiety levels than low monitors. With respect to immediate responses to test result disclosure, we believed that the effects of carrier status on distress would be moderated by coping style. Specifically, we expected to find a significant interaction effect between mutation status and coping style, such that monitoring would be most strongly related to psychological distress among carriers. As mentioned, past studies focusing on short-term changes in BRCA1/2 genetic testing distress levels involved participants who were already members of familial cancer registries (Croyle et al, 1997; Lerman et al., 1996) and who were not naive to genetic testing or the potential implications of testing positive for a mutation. As such, these studies may have underestimated the distress outcomes likely to be observed in a setting with a more variable risk profile, which could allow for greater detection of the influence of coping style. Thus, in addition to assessing coping style, this is the first study to explore immediate post-counseling changes in distress within a clinical sample.

Method

Participants

The data in this report were obtained from 107 women self-referred to the Cancer Assessment and Risk Evaluation (CARE) program at the Lombardi Cancer Center. To be eligible for CARE, participants had to have a personal and family history of breast/ovarian

cancer that resulted in a minimum 10% prior probability of having a BRCA1/2 mutation, including relatives of individuals who tested positive. The mean (*SD*) age of the women in our sample was 45 (12.5) years (range = 20 to 83). The majority were Caucasian (96%), employed on a full-time basis (54%), married (75%), and college graduates (69%).

The uptake rate of testing among probands in the CARE program was presented in a recent report and found to be 82% (Schwartz et al., 2000). As the outcomes of interest pertained to knowledge of one's BRCA1/2 genetic test result, only women who elected to receive their results were included in our analysis. In the final sample, 38 women (36%) were probands affected with breast and/or ovarian cancer (these were the initial members of the family who sought BRCA1/2 testing) and the remaining 69 women (64%) were relatives of probands who tested positive for a BRCA1/2 mutation. Among relatives, 31 (45%) were determined to be mutation carriers and 38 were noncarriers (55%). Thus, the ratio of carriers:noncarriers in our sample was approximately 2:1 (69 to 38).

Procedure

Persons who contacted the CARE program were screened by telephone to determine eligibility. Eligible participants completed a structured telephone interview which included an assessment of their sociodemographic background, cancer family history, and coping style. Following this interview, participants were invited to attend an individual education session which lasted approximately one and a half hours and was led by a genetic counselor. Immediately prior to the education session, participants completed a state anxiety measure (baseline). All pre-test education sessions included qualitative risk assessments based upon personal and family history, details about the process of testing for BRCA1/2 mutations and

interpretation of test results, cancer risks associated with BRCA1/2 gene mutations, options for cancer prevention and surveillance, a discussion of the benefits and risks/limitations of testing, and information about the possible psychosocial impact of testing.

Following the education session, participants were offered the opportunity to provide a blood sample for BRCA1/2 mutation analysis (written consent required). When test results became available, women were invited to an individual disclosure session which was scheduled at the participant's convenience ($Md = 56$ days). At the disclosure session, a more detailed discussion was undertaken regarding test result interpretation and other issues raised during pre-test education. In the present study, 16 women were unable to attend the disclosure session in person and elected to receive their test results and counseling by telephone. Study outcomes did not differ based on the method of test result disclosure (in person or via telephone).

For all of the women included in this report, state anxiety level was reassessed immediately before (pre-disclosure) and after (post-disclosure) the result disclosure session. Thus, the two timeframes of interest were changes in anxiety from baseline to immediately prior to disclosure of BRCA1/2 test results (anticipation period), and from pre-disclosure to immediately following the disclosure session (immediate impact period).

Measures

Dependent Variable

State anxiety. The 20-item State Anxiety subscale of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1983) was used to assess transitory anxiety at three points in time: baseline, pre-disclosure, and post-disclosure. The STAI is self-report measure of anxiety that is reliable, sensitive to change, resistant to practice effects, and has been successfully

used in other reports of the psychological impact of genetic testing (Croyle et al., 1997). Summary scores range from 20 to 80, with higher scores indicating greater anxiety. Internal consistency estimates for the present sample were acceptable at each of the three assessments (coefficient alphas $\geq .90$).

Independent and Control Variables

Sociodemographic characteristics. Participant age, race, education, and marital and employment status were assessed by interview prior to the education session.

Cancer or cancer-related surgical operation history. Similar to Croyle and colleagues (1997), we created a single variable reflective of responses to several interview questions that indicated whether or not the participant self-reported a positive breast and/or ovarian cancer history or had their breasts or ovaries removed.

Coping style. The 32-item Miller Behavioral Style Scale (MBSS) was used to assess dispositional coping style (Miller, 1987; Miller & Mangan, 1983). The instrument is comprised of four hypothetical stress situations; half are in response to a physical threat, the other half to a nonphysical threat. Following each scenario are eight coping statements: four information-seeking ("monitoring") options and four information-avoiding or distracting ("blunting") options. Scores are summed on separate monitoring and blunting subscales and can range from 0 to 16; higher scores indicate more monitoring or blunting. Consistent with the MPM and other published studies examining similar outcomes, we classified participants as high or low monitors on the basis of monitoring scores alone (Miller, 1987; Miller, Roussi, Caputo, & Kruus, 1995; Schwartz et al., 1995). The Kuder-Richardson formula 20 internal consistency reliability of the monitoring subscale of the MBSS was .66.

Results

Anxiety Levels

The mean scores on the state anxiety measure at baseline, pre-disclosure, and post-disclosure were 34.6 ($SD = 8.7$, range = 23 to 57), 38.6 ($SD = 10.7$, range = 23 to 72), and 36.6 ($SD = 11.2$, range = 23 to 70), respectively, and fell within normal limits. All three scores were moderately correlated with coping style ($r = .24$, $r = .33$, $r = .20$, all p 's $< .05$), suggesting that participants with higher monitoring scores tended to be more anxious at each point measured in the study.

The results of the bivariate analyses of predictors of state anxiety at the two time points of interest are shown in Table 1. Pre-disclosure anxiety was associated ($p < .10$) with age, education level, cancer history, and coping style. Specifically, younger women, college graduates, persons who had never been diagnosed with cancer or undergone a cancer-related surgery, and high monitors were more anxious during the anticipatory period. In terms of post-disclosure anxiety, those who graduated from college and those informed of their positive mutation status were more anxious.

Multivariate Analyses of Anxiety Levels

Anticipation. To identify factors having independent associations with anxiety, predictor variables with $p < .10$ associations in the bivariate analyses were tested using multiple linear regression with hierarchical variable entry (Table 2). After controlling for the effects of age, education, cancer history, and baseline anxiety, coping style (entered as a continuous variable) had a significant effect on pre-disclosure anxiety, $\beta = .67$, $p = .03$, $\Delta R^2 = .03$. Higher monitoring scores were associated with greater increases in psychological distress levels while waiting for

test results (Figure 1). These analyses were re-run controlling for potential correlations among family members using generalized estimating equations (GEE; Diggle, Liang, & Zeger, 1994) and the results were essentially unchanged.

Immediate impact. In a second model, we examined predictors of post-disclosure anxiety. After controlling for the confounding effects of education and pre-disclosure anxiety, mutation status had a significant effect on post-disclosure anxiety, $\beta = 11.2$, $p = .0001$, $\Delta R^2 = .22$. Specifically, carriers exhibited more distress after learning their results than noncarriers (Figure 1). The Coping Style main effect and Coping Style x Mutation Status interaction terms were nonsignificant. Again, GEE regression models produced highly similar results.

Discussion

The data presented in this paper highlight two important and complementary findings. The first is that during the period of time while BRCA1/2 genetic testing participants awaited test results, their level of psychological distress varied depending upon their coping style. Specifically, after we controlled for the effects of key confounder variables, women with higher monitoring scores tended to report more anticipatory anxiety than women with lower monitoring scores. The second finding is that immediately after participants were informed of their mutation status, carriers were significantly more distressed than noncarriers regardless of their coping style.

Regarding the anticipation of test results, the short-term distress outcomes shown here are consistent with predictions made by the MPM. Specifically, persons who closely attend to threat-relevant cues within their environments are more likely to experience distress when

confronted with ambiguous situations, such as when more information about cancer risks must be obtained (Miller, 1995; Miller, Roussi, Altman, Helm, & Steinberg, 1994). To the extent that high monitors were less able to disengage from distressing thought patterns that might have been associated with this event (e.g., expecting to receive a positive test result), the anticipatory period was characterized by increased general distress levels. In our study, the level of anticipatory anxiety reported by high monitors was, on average, 10% higher than it was for low monitors. Though modest in magnitude, it nevertheless suggests that the coping style of BRCA1/2 participants may be an important predictor of intermediate psychological outcomes.

On the other hand, the prediction regarding the moderating role of coping style on the impact of mutation status was not supported. The multivariate models indicated that women who learned they were carriers of BRCA1/2 mutations experienced significantly more distress in the post-disclosure period than did noncarriers, and this effect was not modified by coping style. The distress result is consistent with data-based findings of the short-term impact of carrier status on participants' anxiety levels (Croyle et al., 1997). However, the reason why high and low monitoring did not further distinguish the impact carrier status had on these outcomes remains unknown, though several possible explanations exist.

One explanation is that learning that one is a carrier of a BRCA1/2 mutation is a naturally anxiety-provoking stressor for most individuals, and that this response is relatively independent of one's disposition to monitor or blunt in the face of health threats. Unaffected women who carry a BRCA1/2 mutation have a 55 to 85% lifetime risk of breast cancer and a 15 to 65% risk of ovarian cancer (Easton, Ford, Bishop, & The Breast Cancer Linkage Consortium [BCLC], 1995; Ford et al., 1998, Struwing et al., 1997). Among women affected with breast cancer, those with BRCA1/2 mutations are believed to have a 50 to 65% cumulative risk of second

primary (i.e., contralateral) breast cancers and an elevated risk of ovarian cancer (BCLC, 1999; Easton et al., 1995). Thus, the degree of threat facing a woman who receives a positive test result may be high enough to cause transient increases in anxiety regardless of coping style.

A second and related explanation for this finding is that being informed that one is not a carrier of a BRCA1/2 mutation leads to a reduced risk estimate and a diminished threat. As coping style is conceptualized to exert its influence primarily under conditions of health threat, it stands to reason that if the health threat is removed (or substantially reduced) one would not expect to see effects of coping style.

A third explanation is that the effect of the style of coping measured in this study (e.g., dispositional monitoring) may not be observable immediately after learning one's results, though it might be evident at a later point in time. Perhaps greater differences in the patterns of psychological distress of high and low monitors would have been evident after more time had elapsed since the disclosure session took place. The median amount of time between baseline and pre-disclosure (anticipation period) was approximately two months, and coping style effects were seen. In the immediate impact period, this timeframe was reduced to approximately one hour (i.e., the estimated length of time of a disclosure session), which may have been insufficient to detect such effects. It is possible that the distress reported by low monitors may diminish more rapidly as they are better able to cognitively distance themselves from the counseling experience. Given the relatively small sample size employed here, statistical power was likely to be an issue as well.

The results of this investigation have important clinical and practice implications. For certain participants (e.g., high monitors) the anticipation period appears to be a particularly stressful time. Pre-identification of individuals prone to experience heightened distress could be

accomplished through psychological screenings focusing on mood, coping style, and personality functioning. Findings from these abbreviated assessments might then be incorporated into the pre-test education and genetic counseling session, where the information presentation format could be varied (e.g., with written materials, videos, etc.), the intensity of the counseling modified (e.g., to discuss stress-reducing strategies), and intermittent provider contact might be enhanced (e.g., follow-up telephone calls while awaiting test results), to match the needs of the individual participant. For those who report emotional distress and/or difficulty coping while awaiting their results, referrals for psychological management can be arranged as well. In terms of the immediate impact period, our study also suggests that a substantial segment of the sample experienced persistently elevated distress levels immediately before and after receipt of their BRCA1/2 test results. Prior work has shown that high distress interferes with the comprehension of the personal risk estimates presented during cancer risk counseling (Lerman et al., 1995). Among BRCA1/2 carriers, options regarding preventive measures, including decisions about prophylactic surgery, are often re-explored at that time. To the extent that elevated distress interferes with comprehension of the complex information presented during a genetic counseling session, the goals of counseling to help manage medical and family issues (e.g., risk communication) might not be realized.

In evaluating our results, it is important to keep in mind that all women were participants in a BRCA1/2 genetic testing research program. They received comprehensive individual genetic counseling and BRCA1/2 mutation analysis at no cost. Further, all completed extensive epidemiological and behavioral interviews and were monitored closely throughout this process. Such highly structured research environments are almost always susceptible to a number of experimental biases, including self-selection bias and limited external validity. Despite the fact

that these participants were not members of a hereditary cancer registry as in previous studies, the high number of relatives of positive probands (64%) may have enhanced the carrier rate in this sample, and positively influenced their distress levels. Finally, as distress levels were not assessed between baseline and pre-disclosure, or between pre- and post-disclosure, it is not clear whether participants' distress levels peaked at these times, or remained elevated throughout. It is possible, and quite likely, that greater variability characterized their distress over time, especially during the anticipation period.

These limitations notwithstanding, the results provided in this report highlight the fact that anticipatory anxiety among high monitors may be expected to occur prior to BRCA1/2 test result disclosure. Immediately after disclosure takes place, the anxiety reactions of carriers and noncarriers differ substantially, with little observable impact of coping style. Along with the research implications of these results for the MPM, the findings suggest that professionals working with BRCA1/2 testing populations may consider coping style variations to better prepare participants to anticipate their immediate emotional reactions to the genetic testing process, especially in light of positive results. Coupled with prior reports on the short-term distress of BRCA1/2 participants, our findings continue to guide and inform the discussion about safe and effective genetic testing for breast/ovarian cancer patients and their relatives.

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Table 1

Bivariate Analyses of Anxiety Outcomes

Factor	Level (n)	Pre-	<i>t</i> (df)	Post-	<i>t</i> (df)
		disclosure		disclosure	
Age ^a	< 44 Years old (53)	40.7 (10.8)	2.1 (105)**	38.1 (11.5)	1.4 (105)
	≥ 44 Years old (54)	36.4 (10.3)		35.1 (10.9)	
Marital status	Not married (27)	37.6 (11.5)	-0.5 (105)	36.1 (11.0)	-0.3 (105)
	Married (80)	38.9 (10.5)		36.8 (11.4)	
Education level	< College graduate (33)	35.3 (9.5)	-2.1 (105)**	32.9 (10.3)	-2.3 (105)**
	≥ College graduate (75)	40.0 (10.9)		38.2 (11.3)	
Cancer history ^a	Unaffected (52)	40.4 (11.7)	1.8 (105)*	35.6 (11.3)	-0.9 (105)
	Affected (55)	36.8 (9.5)		37.5 (11.2)	
Mutation status	Noncarriers (37)	37.3 (10.5)	-0.9 (105)	28.4 (5.1)	-7.9 (103)***
	Carriers (70)	39.2 (10.8)		40.9 (11.2)	
Coping style ^b	Low monitors (50)	36.3 (9.9)	-2.1 (105)**	35.4 (11.1)	-1.0 (105)
	High monitors (57)	40.6 (11.1)		37.6 (11.3)	

Note. Data are *M* (*SD*). ^aPertaining to breast and/or ovarian cancer. ^bBased on median-split.

p*<.10. *p*<.05. ****p*<.01.

Table 2

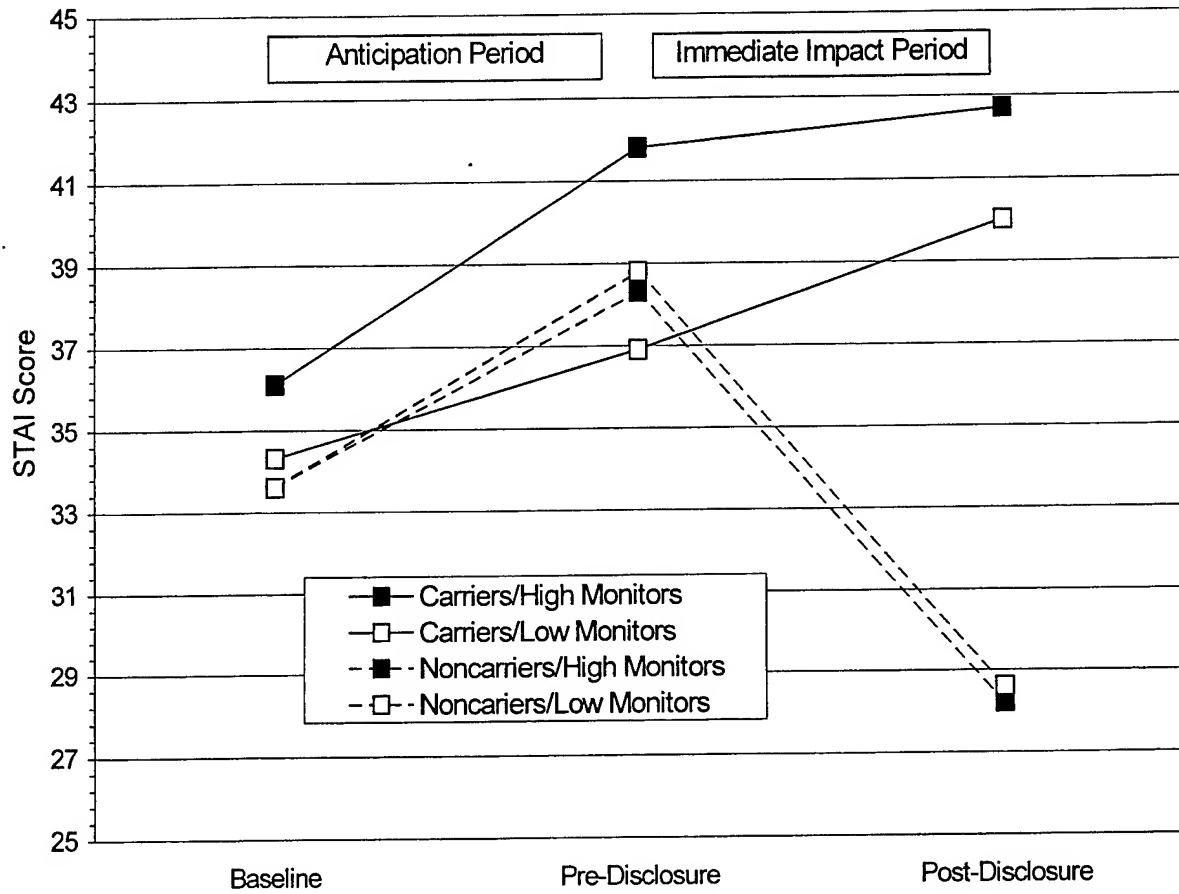
Hierarchical Multiple Regression Analysis of Anxiety Outcomes

Criterion, step, and predictor		ΔR^2	ΔF	Final β
Pre-disclosure anxiety (anticipation)				
1	Age			-0.06
	Education			4.08*
	Cancer history			-4.12*
	Baseline anxiety	.41	17.81**	0.68**
2	Coping style	.03	1.05	0.67*
Post-disclosure anxiety (immediate impact)				
1	Education			2.45
	Pre-disclosure anxiety	.37	30.60	0.61**
2	Coping style			-0.03
	Mutation status	.22	14.24**	11.18**
3	Coping style x mutation status interaction	.004	0.22	0.31

* $p < .05$. ** $p < .01$.

Figure Caption

Figure 1. Mean state anxiety scores at baseline, pre-disclosure, and post-disclosure.. STAI = State-Trait Anxiety Inventory.



The Art of Oncology:

BRCA1/2 Testing—Complex Themes in Result Interpretation

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Supported by Department of Defense Grant DAMB 17-96-C-6069, Grant R01 HG76749
from the National Human Genome Research Institute, Grant R01 CA74861-03 from the
National Cancer Institute/National Institutes of Health, and institutional funds from the
Lombardi Cancer Center

Portions of this manuscript were presented during a poster session at the American
Society of Clinical Oncology annual meeting, May 23, 2000 in New Orleans, Louisiana

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INTRODUCTION

One of the most exciting and highly anticipated breakthroughs in cancer genetics was the cloning of BRCA1 and BRCA2 (BRCA1/2) in 1994 and 1995.^{1,2} Since that time, it has been interesting to observe the spectrum of experiences that have occurred as cancer genetic counseling and testing have permeated research and clinical settings. Prior to these events, predictive testing could be performed only by linkage analysis, which yields a probability about whether one carries a gene "marker." Scientists and clinicians struggled to determine whether to disclose these types of results to patients and if so, what "margin of error" was acceptable.³ Dramatic examples of life altering decisions were published, setting the bar for the anticipation that would ensue about the promise of genetic testing for breast cancer risk. For example, in 1992, a healthy woman who found out that she had a 98% chance of not carrying her family's BRCA1 marker was spared from having prophylactic mastectomy days before the surgery was scheduled to occur.³ In the same family, a 40-year-old woman who learned she had the BRCA1 marker rushed to have her first mammogram in two years, only to learn that a 6 mm malignant tumor was present – small enough that her chance of cure was very high.³

Now, several years after BRCA1 and BRCA2 were cloned, we have a better understanding of the pertinent scientific and psychosocial issues, but are still faced with many of the complexities and uncertainties we encountered earlier. We know that patient decision-making about genetic testing and how to utilize such information is not a simple process. Even when a positive result (i.e., a deleterious mutation) is identified, the associated cancer risks cannot be precisely quantified and the efficacy of management options is still very uncertain.⁴⁻⁶ And when a negative result is obtained, it could be good news fraught with survivor guilt (in the case of a true negative for a familial mutation), or

as this paper focuses on, a negative result could be completely ambiguous and raise more questions than it answers. Addressing this issue is especially important because a significant proportion of high-risk families do not harbor deleterious mutations in BRCA1 or BRCA2. For example, studies have demonstrated that 16-66% of high-risk families do not carry detectable mutations in these genes.⁷⁻⁹

Thus, even though interpretation of BRCA1/2 results is relatively straightforward in many circumstances, complex cases are not infrequently encountered in the clinical setting. In such instances, alternative explanations for test results need to be considered, additional family members may need to be tested, or participation in research studies may be indicated. The focus of this paper is to illustrate some of these complex themes in genetic counseling. We present five vignettes based on actual cases drawn from our clinical research program, through which high-risk individuals receive genetic counseling and testing at no cost. These vignettes and pedigrees have been modified to protect patient and family confidentiality. The commentaries following each case highlight concepts that can be applied globally to the process of cancer risk counseling.

Case 1: Surgical decision-making in a newly diagnosed breast cancer patient

Insert figure 1 about here

Presentation

The proband, AB, was a 51-year-old woman of Ashkenazi Jewish descent who was recently diagnosed with a small single focus of DCIS in her right breast. The only treatment she had had at the time of her initial genetic counseling session was a wide re-

excision with clear margins. Her family history, depicted in figure 1, was remarkable for her sister, diagnosed with early onset breast and ovarian cancer, and her mother, who had ovarian cancer at age 50. Her paternal history was non-contributory. AB was informed by her surgeon that she was a candidate for breast conserving therapy; however, in light of her family history, she was planning to have bilateral mastectomies regardless of her BRCA1/2 test results.

AB was tested for the three mutations found with increased frequency in Jewish individuals (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2).¹⁰ These results are generally available within one to two weeks, although the turnaround time may vary by lab. The three BRCA1/2 mutations mentioned above account for the vast majority of those observed in high-risk Ashkenazi Jewish families;⁸ however, none of these mutations was identified in AB. Given that she had such a strong family history of breast/ovarian cancer, and because these mutations are found with such high frequency in families such as this, the genetic counselor suspected that she may have developed sporadic breast cancer within a hereditary breast cancer family. Thus, because AB was planning to undergo surgery relatively soon, we thought it was advisable to offer BRCA1/2 testing to her affected sister. AB said that her sister would probably be receptive to this option. Subsequently, she was encouraged to contact her sister and if she did decide to pursue testing, we suggested that AB await these results before proceeding with surgery.

AB's sister promptly participated in our genetic counseling and testing program, and indeed tested positive for a BRCA1 mutation (5382insC). She immediately shared this result with AB, and at this point, about one month had elapsed since AB's initial genetic counseling session. Based on her sister's results, we concluded that AB's breast

cancer did occur sporadically and her risks for ipsilateral and contralateral breast cancers were the same as those encountered by other women with breast cancer in the general population. In considering this information, she did not opt for bilateral mastectomies, but she did proceed with radiation therapy as recommended by her physicians. In addition, this result indicated that, despite her family history of ovarian cancer, AB was not at high risk for this cancer. Also, her children were reassured about their cancer risks. Although AB's sister opted to get tested primarily for the sake of gaining information for AB, there were medical implications to her with respect to contralateral breast cancer risks. This was an important consideration for her because she was in good health and had no evidence of disease. In addition, testing would now be informative to many at-risk relatives such as AB's sister's adult children, her other siblings, and her maternal cousins.

Commentary

This case presents a striking example of how genetic counseling and testing altered the course of surgical cancer treatment and spared a newly diagnosed breast cancer patient from having extensive breast surgery. The proband, AB, thought initially that genetic testing would not impact her surgery decision because she believed that she would be at high risk regardless of whether she tested positive or negative. However, there is an important distinction between an affected proband who tests negative for BRCA1/2 mutations, yielding an uninformative result (for example if AB tested negative and we were never able to test her sister) versus a proband who obtains a "true negative" result, as in this case. In order to make this pivotal determination, it was worthwhile for the patient to make a surgical decision only after waiting to obtain not only her results, but her sister's results as well. In general, results for the panel of common mutations is

available sooner than full sequencing, which may take about 3 weeks.¹¹ For some patients, such as those ascertained immediately after diagnosis, or who are undergoing neoadjuvant or adjuvant chemotherapy prior to radiation therapy, this timeframe is usually acceptable.

This case also illustrates the importance of collecting a detailed family history and evaluating it carefully to determine who has the highest a priori chance of testing positive, although in AB's family, both she and her sister had very high probabilities of testing positive. Models assessing carrier probability are available which are generally designed for clinical application.^{8,12-14} For example, the BRCAPRO model based on the work of Parmigiani et al¹⁴ predicted AB's probability of carrying a BRCA1 or BRCA2 mutation to be .93, with her sister's probability being 1.0,¹⁵ although in practice, it is unwise to counsel that the probability of testing positive is as definitive as 100%. The sister's risk was higher because she had both breast and ovarian cancer and because she was young when diagnosed with these cancers. However, the BRCAPRO model does not distinguish between invasive and noninvasive breast cancer. The sister's prior probability of testing positive is lower (at 71%) when AB's cancer history is excluded, according to the model by Frank and colleagues.⁸ In light of these considerations, if AB had not been faced with an imminent surgical decision, it would have been prudent to offer testing to her sister first.

In general, BRCA1/2 probabilities obtained from mathematical models should be considered in combination with traditional pedigree-based (i.e., qualitative) assessments which take into account the family structure; factors that may affect penetrance and variable expression within the family; non-breast, non-ovarian manifestations of BRCA1/2 mutations (such as prostate and pancreatic cancer^{10,16}); and the possible

existence of other hereditary cancer syndromes. In addition, data regarding pathological features of BRCA1/2 tumors are sometimes helpful in determining whom to test first or the likelihood of obtaining a positive result. Although mathematical calculations based specifically on the pathological findings of affected individuals can be utilized,^{17,18} some qualitative factors are relatively easy to integrate into routine risk assessment. For example, germ cell tumors of the ovary occur often in young women¹⁹ but because they are non-epithelial, they are not thought to be associated with BRCA1/2 mutations, in which epithelial cancers, namely serous adenocarcinomas, dominate the tumor spectrum.^{20,21} With respect to breast cancer pathology, several studies have shown that medullary carcinomas occur in excess in women with BRCA1 mutations.²² In addition, some studies have shown that certain tumor types may occur less frequently in women with hereditary breast cancer. For example, studies have demonstrated that DCIS is less common in BRCA1/2 carriers compared to sporadic cases; nonetheless, it may still be observed.²³⁻²⁵

The issues surrounding genetic counseling and testing in newly diagnosed breast cancer patients are receiving increasing attention in the clinical arena. All women who have had breast cancer have an increased risk of developing a new primary breast cancer, regardless of whether they have had breast conserving therapy or a unilateral mastectomy.²⁶ However, when a BRCA1 or BRCA2 mutation is identified, these risks are substantially elevated. Although the risk for ipsilateral breast cancer is not clearly defined in women with hereditary breast cancer, the risk does appear to be elevated over long follow-up periods.²⁷ Continuing study in this area is very important to obtain more precise information.²⁸ On the other hand, the increased risks for contralateral breast

cancer are well established.^{8,29-33} These risks are generally quoted as lifetime risks of approximately 50% (BRCA2) and 65% (BRCA1).^{16,29,30}

With respect to local treatment, although theoretical concerns exist about the potential adverse effects of radiation therapy in carriers,^{34,35} Pierce and colleagues³⁶ did not find evidence of increased radiation sensitivity or sequelae in carriers. As this question and the issue of long term survival continue to be assessed, there is concomitant investigation into the efficacy and appropriateness of different surgical options for carriers.^{37,38} Thus, in the absence of formal recommendations, and in considering their risks for second cancers, newly diagnosed breast cancer patients who test positive for a mutation in BRCA1 or BRCA2 may opt for more aggressive surgical procedures. This decision may be based in part on data showing that bilateral mastectomies substantially reduce the risk of breast cancer in high-risk women, including carriers.^{39,40} However, because many carriers are less than age 50 at diagnosis,^{7,29,30} an age group in which breast conservation therapy is often a preferred option and is thus performed frequently,^{41,42} more extensive surgery may not be desirable. It is thus encouraging that in addition to the ample evidence that tamoxifen reduces the risk of contralateral breast cancer in unselected patients, data also suggest that tamoxifen may offer protection against contralateral breast cancer in women with a BRCA1 or BRCA2 mutation.^{43,44} For carrier breast cancer patients who would not be recommended to take tamoxifen based on the characteristics of their tumor (e.g., because it is estrogen receptor negative), decision-making may be especially complicated. Further research about the optimal treatment for newly diagnosed breast cancer patients who carry mutations in BRCA1/2 as well as the psychosocial impact of obtaining this information is critical to help guide patients and providers through the process of genetic counseling and medical decision-making.

Case 2: Interpreting full negative BRCA1/2 results

Insert figure 2 about here

Presentation

CD had a history of left-sided breast cancer diagnosed at age 41, for which she underwent a unilateral mastectomy. Her paternal family history, as shown in figure 2, was significant for six cases of breast cancer in three generations, including four early onset cases (i.e., diagnosed before age 50), one case of bilateral breast cancer, and one male breast cancer. Her maternal history was not significant. The proband underwent full sequencing of BRCA1 and BRCA2, and no mutations or variants were identified. Given the strength of the family history, this result was considered to be uninformative as hereditary breast cancer could not be ruled out. Therefore, women in this family still need to be vigilant about breast cancer screening and aware of possible options for risk reduction, based on the guidelines in table 1^{5,45-47}. In addition, men should also be informed about potential breast cancer risks.

Insert table 1 about here

Commentary

The proband in this family was predicted by one model to have a probability of .90 of harboring a BRCA1 or BRCA2 mutation, although this may still be an underestimate because the model does not account for third-degree relatives (i.e., cousins).¹⁵ In particular, this family history is strongly suggestive of mutations in the

BRCA2 gene, which confer a 55-85% risk of female breast cancer and a 15-25% risk of ovarian cancer, as well as an increased risk for male breast cancer.^{7,10,29,30,48} While the lifetime breast cancer risks in BRCA1 and BRCA2 carriers are comparable, overall, BRCA2 mutations are associated with a lower risk of ovarian cancer than BRCA1 mutations, and also appear to be more strongly associated with male breast cancer.^{7,29,30,48,49} Therefore, because sequencing is not 100% sensitive, the proband may have a BRCA1 or BRCA2 abnormality such as a large deletion, a mutation in a regulatory region, or a splice variant that could not be detected by this method.^{50,51} Technical specifications from Myriad Genetic Laboratories indicate that these types of abnormalities result in an estimated 5-15% of BRCA1/2 mutations being missed by sequencing.¹¹ For example, in Dutch families, large genomic BRCA1 deletions are found with increased frequency and would be missed by usual methods of mutation screening.⁵² In another study, 42 American families with breast and ovarian cancer and no detectable BRCA1/2 mutations were retested using PCR and Southern blotting.⁵³ Five families (12%) were found to have an exon duplication or other genomic rearrangement in BRCA1.⁵³

Another possible explanation for CD's result is that she has a mutation in another breast cancer susceptibility gene. Other hereditary breast cancer syndromes such as Li-Fraumeni and Cowden disease should be considered; however, because this family contains only cases of breast cancer, testing for mutations in the associated genes (p53 and PTEN, respectively) is not strongly indicated. Specifically, criteria for the diagnosis of Li-Fraumeni syndrome include the presence of a sarcoma diagnosed less than age 45, as well as breast and possibly other cancers,⁵⁴ and operational diagnostic criteria for Cowden syndrome indicate that features other than breast cancer should be present, such

as mucocutaneous or thyroid lesions (e.g., follicular carcinoma)⁵⁵. Thus, in this family, if a mutation in another gene exists, it is likely to be in a gene that has not yet been localized.

Finally, the possibility must be considered that CD's cancer represents a phenocopy, or a sporadic case within a hereditary breast cancer family. Although this explanation does not seem probable given that she was diagnosed at the youngest age within the family and is a first-degree relative of a male breast cancer case, it cannot be completely excluded. In instances such as this, it is reasonable to offer full BRCA1/2 sequencing to one of CD's affected cousins. If one of the cousins were to test negative, the chances become highly unlikely that both tested women in this family developed sporadic breast cancer. Further, because there are three living women affected with breast cancer and several unaffected individuals, it is appropriate to make a referral to additional research studies, such as those offering indirect approaches to BRCA1/2 mutation screening (e.g., using linkage analysis, which has been informative in some families when no mutation has been identified).⁵⁶ In addition, the proband's DNA may be reanalyzed using techniques such as Southern blotting, which can detect genomic rearrangements in BRCA1/2.⁵³ It is also hoped that new technologies, such as the "conversion" approach (in which the two copies of a gene are separated for analysis), may help increase the sensitivity of existing means of mutation detection.⁵⁷ With respect to novel genes, this family and others like it could be instrumental in identifying new breast cancer susceptibility loci, such as the putative locus on 13q21.⁵⁸

Case 3: Clarifying the significance of genetic variants

Insert figure 3 about here

Presentation

EF was diagnosed with unilateral breast cancer at age 48, for which she was treated with lumpectomy and radiation. Her family history was significant for two maternal aunts with post-menopausal breast cancer (see figure 3). Her mother was alive and well at age 70 with no history of cancer or prophylactic breast or ovarian surgery. Her paternal history was non-contributory. EF's test results indicated that a deleterious mutation was not identified in BRCA1 or BRCA2; however, a variant of "uncertain significance" was found in her BRCA2 gene. In other words, this variant could be associated with increased cancer risks or it could represent a benign polymorphism (normal change) in the gene. Because this distinction could not be demonstrated either biologically or empirically, these test results were considered uninformative. Thus, EF could still be at increased risk for developing another cancer, although her personal and family history of breast cancer were not highly suggestive of an inherited predisposition. Because of the uncertainties associated with interpretation of this result and the fact that it should not be used as the basis for making medical management decisions, predictive testing was not extended to at-risk relatives such as the proband's sisters. However, EF's mother was tested and did not have the BRCA2 variant, which meant that the variant was not tracking with the breast cancers in the family (i.e., EF inherited the variant from her father). Subsequently, the variant was identified in a few high risk breast cancer patients who also carried a deleterious mutation in BRCA1 or BRCA2, further decreasing the

likelihood that this variant is risk-conferring. Nevertheless, the proband and her relatives could still be at somewhat increased risk for developing breast cancer, and therefore they may opt for close surveillance, as outlined in table 1^{5,45-47}.

Commentary

As part of the pre-test genetic counseling session and informed consent process, it is important to explain the limitations of testing and the possibility that no mutation will be found due to the presence of an undetected mutation in BRCA1/2 or a mutation in another as yet unidentified gene (see case 2). In fact, the predicted probability of this patient harboring a BRCA1 or BRCA2 mutation was less than 0.10.¹⁵

Patients must also be informed about the possibility that one or more variants in the BRCA1/2 genes may be identified. In our clinical research program, 10% of high-risk probands received ambiguous results (i.e., "variants of uncertain significance") (unpublished data), which is consistent with the observations by Frank et al⁸. As more individuals are tested, and as testing is extended to more ethnically diverse and clinically representative populations, often from families that are not considered to be highly suggestive of hereditary breast cancer, it is likely that the number of individuals found to carry variants will also increase. Just as specific deleterious mutations recur in certain ethnic populations, such as those of Ashkenazi or Icelandic descent,^{10,59} the frequency of reported variants may also be elevated in certain ethnic groups such as African-Americans.⁶⁰

The variant identified in this family is a missense mutation, which means that one component of DNA was substituted for another. It had not been observed previously, and although the mutation occurred in a coding, or functionally important part of the BRCA2

gene, the resulting change in amino acid sequence did not result in a truncated BRCA2 protein—a frequent occurrence with deleterious mutations.^{51,61} Other variants may include mutations in intronic regions or in very distal portions of the gene.¹¹ Some missense mutations are known to be clinically significant, such as C61G and C64G, which disrupt the RING finger (a critical domain of the BRCA1 protein).^{51,62}

However, in the absence of widely available functional tests, the most accessible data about the interpretation of variants arise from clinical observations. For example, if a variant does not track with the breast and ovarian cancers in several families, or if it is seen in conjunction with known deleterious mutations, it can be inferred that the variant is less likely to be of clinical significance.^{11,63} Further, variants may be classified as benign polymorphisms if they are observed in control samples (i.e., from unaffected individuals in the general population), but it is difficult to know what frequency in the controls is sufficient to make that judgment.⁵¹ Nonetheless, when factored into Bayesian computations, these types of observations may also help determine the significance of variants.⁶⁴

In rare instances, if a variant tracks with breast and/or ovarian cancers in several families, is not present in control samples, and the genetic change is likely to be of functional significance (e.g., because it results in the substitution of a highly conserved amino acid that is critical for cell cycle regulation), there may be a high level of suspicion, but not definitive proof, that the variant is risk-conferring.^{51,61,63} From a genetic counseling perspective, explaining this type of result to families is very challenging. In response, we have developed specific educational materials about variants for probands and family members to help explain the interpretation and implications of such results. These materials are especially helpful because on a case-by-case basis, and

with careful consideration of the specific variant involved, it may be appropriate to offer predictive testing to at-risk individuals. As always, pre-and post-test counseling and follow-up are imperative. Because results may then be used for medical management which could include aggressive means of risk reduction in female carriers, and the discontinuation of heightened surveillance in non-carriers, such actions must be undertaken with extreme caution. It is also critical that patients understand that the classification of variants is subject to change as functional tests are developed⁵¹ and that these variants may confer a modified risk for breast and/or ovarian cancer compared to most recognized “deleterious” mutations. In addition to published articles, information about the classification of variants may be found on-line via the Breast Cancer Information Core⁶⁵ and/or through revised reports issued by the laboratory. It is important to maintain current contact information for patients in the event that it is necessary to update them about such new developments.

Case 4: Determining the parental origin of an identified mutation

Insert figure 4 about here

Presentation

GH pursued genetic counseling and testing because her sister, a proband in our program, recently tested positive for a BRCA1 mutation (her BRCA2 gene was normal). GH understood that she was at 50% risk for inheriting the BRCA1 mutation identified in her sister, and in fact, she tested negative for this mutation. However, it was emphasized

that even though she tested negative, we could not state that her cancer risks were reduced to the levels observed in the general population.

In this case, the family history, as depicted in figure 4, was significant for cancer on both sides of the family. There were five cases of breast cancer on the maternal side of the family, with at least three of these occurring at early ages (although records were not available to confirm the diagnoses in GH's maternal grandmother or her siblings). This history was strongly consistent with hereditary breast cancer, and we suspected that the mutation was likely arising from the maternal side. However, on the paternal side of the family, a first cousin (the daughter of an uncle) had early onset breast cancer and GH's grandmother had breast cancer in her 70s. This history is much less compelling than the history on GH's maternal side but because the cousin was diagnosed with breast cancer at a young age, and is linked to GH through two males, it is not out of the question that the mutation could be present on this side of the family. In other words, hereditary breast cancer may be present on both sides of GH's family, but only one side is transmitting the identified BRCA1 mutation. Further complicating matters was the fact that GH's paternal cousin's mother had ovarian cancer. Thus, another possible interpretation is that the cousin's breast cancer may be attributable to a mutation passed down through non-blood relatives to GH. If this were the case, then the breast cancer in GH's paternal grandmother very likely occurred sporadically.

In order to determine which side of the family carried the mutation, the following steps were undertaken:

- 1) Testing for the single BRCA1 mutation was offered to GH's maternal aunt with breast cancer (see figure 4). Consistent with our clinical interpretation, the BRCAPRO model, while it could not capture the entire structure of the proband's family, predicted that the

aunt had a very high chance of testing positive, whereas the cousin's chance was significant, but much lower.¹⁵ The aunt's results revealed that the BRCA1 mutation was ruled out. Full sequencing of BRCA1 and BRCA2 was then performed, which did not reveal the presence of a mutation. Explanations for this result, as discussed in case 2, include the possibility that GH's aunt developed sporadic breast cancer or that the BRCA1 mutation identified in her niece was inherited from the other (paternal) side of the family. In either instance, hereditary breast cancer on GH's maternal side was not ruled out.

- 2) Testing GH's maternal uncle was also a possibility, but he declined to be tested.
- 3) GH's paternal cousin with breast cancer was offered testing for the single BRCA1 mutation, but she also declined to be tested.

Therefore, because it could not be determined in which side of the family the BRCA1 mutation was segregating, and/or whether another mutation was present, GH was offered the opportunity to undergo additional genetic testing consisting of full BRCA1/2 analysis. However, due to cost concerns (this additional testing was made available clinically) and the strong possibility that a distinct mutation would not be present in her, she did not pursue that option. Thus, GH was counseled that she still may be at increased risk for breast cancer, and may also have an increased risk for other cancers such as ovarian cancer. She opted to continue with close surveillance and to consider options for chemoprevention.

Commentary

Although hereditary breast cancer is a rare occurrence, accounting for only up to 10% of all breast cancers,⁶⁶ in many instances, individuals will have family histories on

both sides that are suggestive of an inherited predisposition. As in this case, one side of the family appeared to be more compelling than the other side. When attempting to determine from which side of the family a mutation was inherited, it may be necessary to extend testing to family members. In some cases, it may be feasible to perform single mutation analyses on archived paraffin-embedded tumor tissue from affected relatives who are deceased, although there are limitations in this process.⁶⁷ Acquiring the tumor block from GH's mother was not possible because she was diagnosed over thirty years ago, but if she had been diagnosed more recently, testing her tumor tissue for the single BRCA1 mutation may have been an option. In other instances, offering testing to unaffected individuals may be warranted (e.g., GH's maternal uncle). Although this process can be time consuming if there are several unaffecteds in the family, the practice is sometimes fruitful.

Once a mutation is identified in a family, the standard practice is to test relatives only for the presence or absence of that mutation, except for Jewish individuals, who should be tested for all three founder mutations.^{10,68} Thus, it is tempting to reassure individuals about their cancer risks when they test negative for a familial mutation. However, the interpretation of a test result as "true negative" can be done only when both sides of the family are assessed. In addition, when distant relatives (e.g., cousins) have had cancer, it is critical to inquire about the cancer family history of both of their parents as risk may not be conferred through the bloodline of the person seeking risk information.

If there are features of the family history that raise concern, it is important to counsel individuals that because their risk may be substantially higher than average, screening guidelines for the general population may not be adequate. This principle

applies when both sides of the family are suggestive of the same hereditary cancer syndrome and when other cancer(s) or cancer clusters are present.

Case 5: Re-evaluating risk assessment based on an evolving family history

Insert figure 5 about here

Presentation

In 1997, the proband IJ presented for genetic counseling and testing because she wanted to know why, at age 29, she had been diagnosed with breast cancer, for which she underwent a lumpectomy followed by radiation and chemotherapy. At the time, no immediate family members were affected with breast or ovarian cancer (figure 5). Her paternal family history was not significant for any cases of cancer and her mother's family history, which consisted of many unaffected women, did not appear to be suggestive of hereditary breast cancer even though her aunt was diagnosed with breast cancer at an early age. Of note, IJ reported initially that another maternal aunt had ovarian cancer, but review of medical records indicated that she had undergone TAH-BSO because of uterine bleeding and the presence of benign ovarian cysts diagnosed at age 53. IJ underwent full sequencing of BRCA1 and BRCA2, and no mutation or variants were identified. Therefore, she was counseled that her breast cancer probably developed sporadically, despite her young age at diagnosis. Nevertheless, based on empiric data, she was informed that her sisters' and mother's risk for breast cancer was elevated⁶⁹ and that they should be screened appropriately.

After she received her genetic test results, JJ recontacted the genetic counselor to update the family history. Since 1997, two of her sisters and her mother were diagnosed with breast cancer. Her sisters were diagnosed in their 30s, and their mother was diagnosed in her mid-60s. These diagnoses were confirmed by review of pathology reports. In light of this information (now five cases of breast cancer in two generations), the proband was counseled that the family history had become highly suggestive of hereditary breast cancer. Interestingly, the BRCAPRO model predicted that JJ's *prior* probability of having a BRCA1 or BRCA2 mutation with the revised family history would have been about 0.9.¹⁵ Given that no mutations were identified, the usual potential explanations for uninformative test results were provided, as in case 2. However, given the proband's very young age at diagnosis and the strength of her family history, it became much less likely that our initial impression (i.e., that her cancer occurred sporadically) was correct. Thus, with five living breast cancer cases, this family was referred for further research studies as mentioned in case 2.

Commentary

Previous cases have addressed the complex nature of interpreting uninformative test results, which is also applicable here. However, the crux of this case surrounds the evolving aspects of the family history and how this information affects interpretation of test results. As this case demonstrates, risk assessment is only as accurate as the family history on which it is based. Therefore, it is important to encourage patients to obtain information about their family history from relatives, and to follow-up by requesting confirmation of diagnoses whenever possible. Although review of pathological reports is ideal, in instances when these are not available, review of death certificates can be

helpful. It is not uncommon for cancer diagnoses to be misreported, especially in more distant relatives.⁷⁰ Misreporting may include an incorrect primary site (e.g., colon cancer reported as “liver cancer” or ovarian cancer reported as “stomach cancer”) or confusion between malignant and benign conditions (e.g., benign prostatic hyperplasia reported as “prostate cancer” or ovarian cysts reported as “ovarian cancer”). These types of errors can result in a significant underestimate or overestimate of risk which may affect the screening and prevention guidelines provided to the patient.⁷¹ In particular, because the presence of ovarian cancer is such a strong predictor for the identification of BRCA1/2 mutations,^{8,12} determining the presence or absence of this malignancy is very important.

In addition, because family history does evolve over time, it is prudent for providers of genetic counseling services to encourage a two way line of communication regarding changes in the clinical status of the patient or the family history.⁷² This process helps to ensure that cancer risks are reassessed accordingly and new research developments can be discussed.⁷² Invariably, other breast cancer genes will be identified, and it is likely that the first individuals to partake of new testing options will be those who received uninformative BRCA1/2 results.

DISCUSSION

The vignettes presented in this paper demonstrate that the interpretation of BRCA1/2 results is often not straightforward. However, even within these complex cases, certain themes in risk assessment and result interpretation emerge, as summarized in table 2. Critical components of genetic counseling include a discussion of the many

Insert table 2 about here

medical and scientific issues related to risk assessment and genetic testing, as well as concomitant psychosocial issues.^{73,74} Although the latter was not a focus of this paper, it is important to note that published studies have found that most BRCA1 genetic testing participants do not experience significant adverse psychological effects in the short-term.^{75,76} It is encouraging that both patients and providers believe that the medical and psychosocial aspects of genetic testing are important to address during genetic counseling for hereditary cancer.⁷⁷ A thorough understanding and consideration of this spectrum of issues, including the potential benefits, limitations, and risks of testing can be obtained through the process of informed consent—a process which is folded into the components of pre-test education and counseling.^{74,78,79} Informed consent should also be obtained in writing before any patient undergoes genetic testing.⁷⁴

For patients, the provision of genetic counseling using a multidisciplinary approach can be very effective.⁷⁴ In fact, it has been shown that in addition to working with genetic counselors, patients are interested in having oncologists involved in the delivery of information related to genetic testing.⁸⁰ Similarly, the educational initiatives and recommendations espoused by the American Society of Clinical Oncology (ASCO) strongly affirm the role of clinical oncologists in identifying candidates for genetic testing and in communicating information about the benefits, limitations, and applications of such testing.⁷⁸ The Society also endorses regulatory, legislative, and research efforts to promote safe and effective testing.⁷⁸ Likewise, the Society of Surgical Oncology and the Oncology Nursing Society have also issued position statements advocating clinical and

research efforts and the involvement of their members in the cancer genetic counseling and testing process.^{81,82}

Based on our experience, we realize that the time consuming nature of pre-test and post-test genetic counseling, in addition to its many complexities, may make it difficult for many oncologists to provide comprehensive services at the point when patients are ready to consider genetic testing or to get their results. Therefore, a referral to a cancer genetic counseling provider (i.e., a genetic counselor or a nurse specializing in genetics) is appropriate. However, knowledgeable physicians can offer a great deal of information and support to patients when they ask for recommendations about whether to be tested and how to manage their risk of cancer. This is especially important as most genetics providers are not likely to have ongoing contact with patients, whereas oncologists and oncology nurses see their patients at regularly scheduled appointments for screening or other follow-up. The growing partnership between genetics and other medical specialties has and will continue to enable patients to gain the most potential benefit from cancer genetic testing, and will serve as a paradigm for service delivery once predisposition testing for other adult-onset disorders becomes available.

ACKNOWLEDGMENTS

The authors would like to thank all of the men and women who participated in this study as well as the physicians and nurses who referred patients to us. We are grateful to Dr. Marc Lippman for his support of this study; Camille Corio, MA for performing data management; Annalisa Dialino-Felix, BS for preparing the figures and providing helpful comments; and to Anahita Nikzad, MS for performing BRCAPRO analysis. The clinical research program from which these cases were drawn has received Institutional Review Board approval from Georgetown University Medical Center. In addition, BRCA1/2 gene testing was performed by the Institute for Molecular and Human Genetics at Georgetown University Medical Center, Myriad Genetic Laboratories (special thanks to Dr. Tom Frank, Medical Director), and the University of Pennsylvania Genetic Diagnostic Laboratory.

Table 1: Medical management guidelines for women from high-risk site-specific breast cancer kindreds in which a deleterious BRCA1/2 mutation has not been identified

Breast Cancer:

- Education about breast self-examination, to begin in the 20s
- Clinician-performed exams every 6-12 months beginning by age 25-35
- Annual mammography beginning 10 years younger than the youngest affected relative, to commence between age 30 and 40, whichever is earlier
- Consideration of chemoprevention options
- Consideration of prophylactic mastectomy

Ovarian Cancer:

Screening and prevention options are generally reserved for women with a family history of ovarian cancer, and/or those known to carry a risk-conferring mutation in BRCA1 or BRCA2. In families in which a proband was not found to harbor a deleterious BRCA1 or BRCA2 mutation, and in which no women have developed ovarian cancer, it is unclear whether early detection or prevention measures for ovarian cancer are indicated. Therefore, women from high-risk site specific breast cancer families should discuss the relative benefits, risks, and limitations of screening and prevention options with their physicians.

Based on references 5,45-47

Table 2: Summary of common themes in cancer risk counseling

To provide comprehensive risk assessment:

- Compile a detailed 3-generation pedigree and update periodically as history may evolve over time
- Inquire about both sides of the family for your patient and his/her distant relatives with cancer
- Confirm diagnoses of cancer, precancerous stigmata, or possible related conditions with medical records or death certificates
- Initiate testing with an affected proband if possible, preferably with the highest chance of testing positive (e.g., based on age and/or cancer diagnosis)

To facilitate test result interpretation, it is important to note that:

- More than one affected individual in a family may need to be offered testing
 - Sporadic cases of cancer, especially breast cancer, may occur within BRCA1/2 families
 - The absence of a deleterious mutation in an affected proband does not definitively rule out hereditary breast cancer
 - The significance of variants may be clarified by clinical observations within families and/or functional tests
-

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FIGURE LEGENDS

Figure 1: Surgical decision-making in a newly diagnosed breast cancer patient

Figure 2: Interpreting full negative BRCA1/2 results

Figure 3: Clarifying the significance of genetic variants

Figure 4: Determining the parental origin of an identified mutation

Figure 5: Re-evaluating risk assessment based on an evolving family history

Ashkenazi Jewish

Ashkenazi Jewish

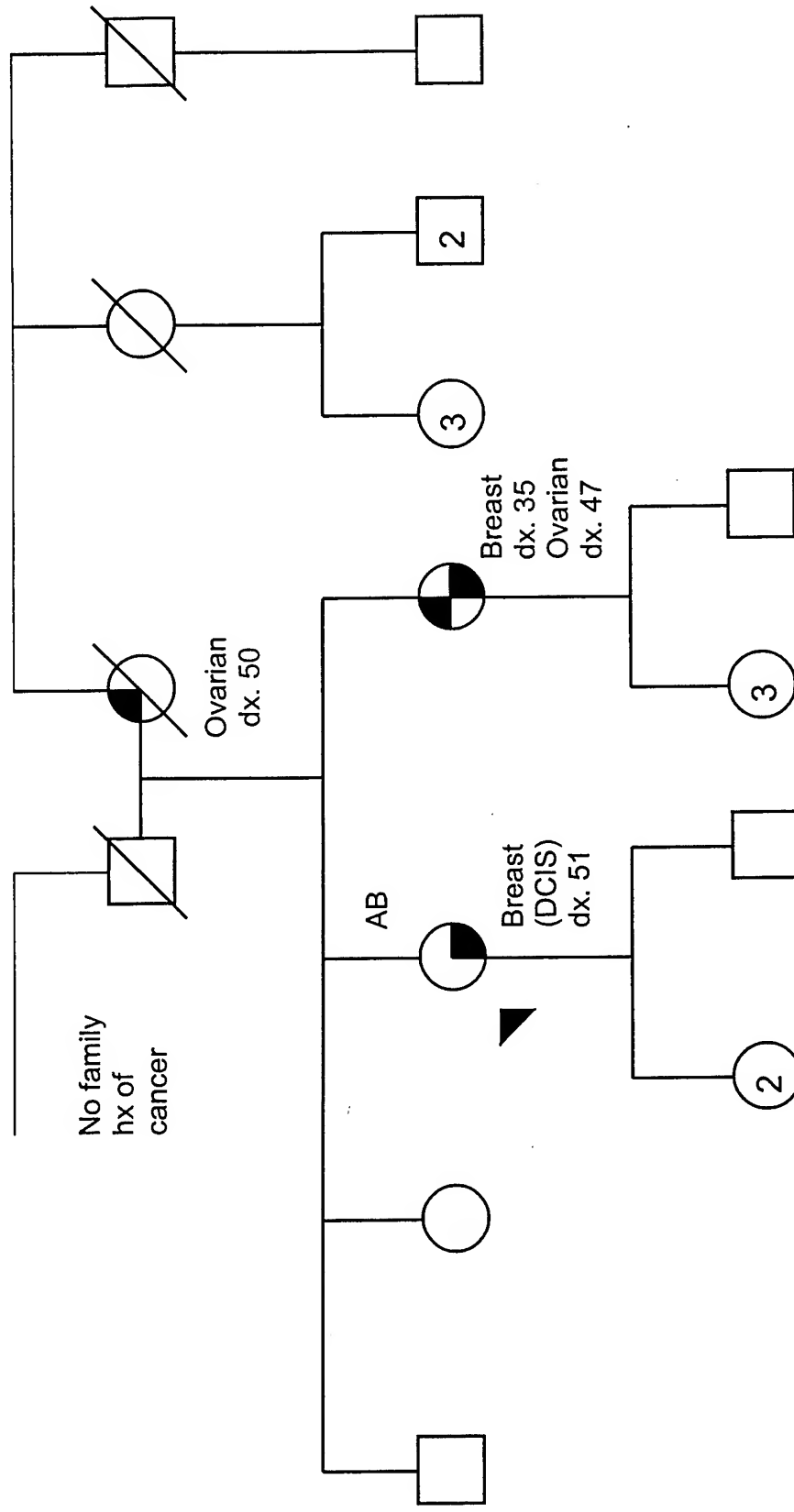


Figure 1

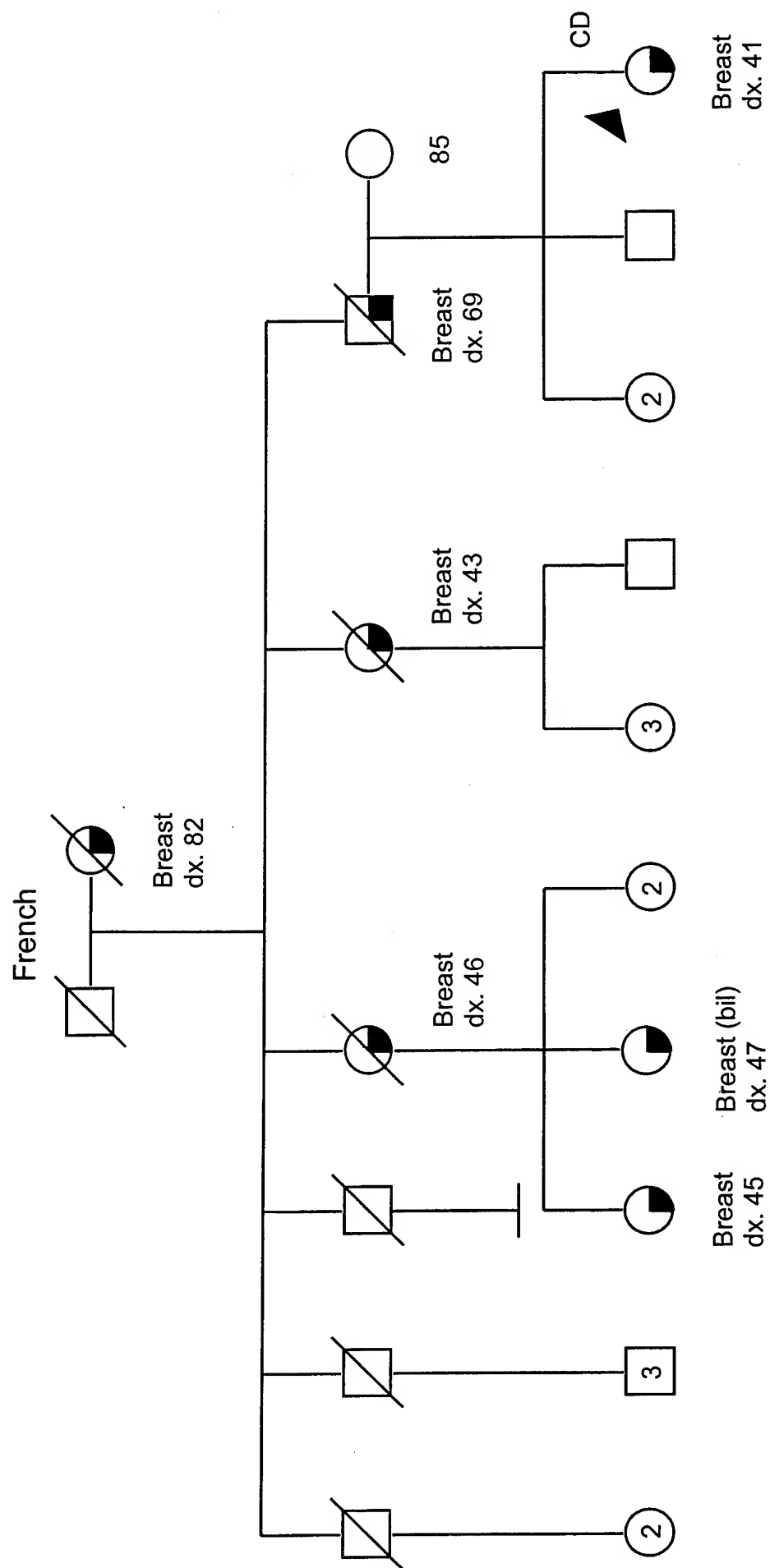


Figure 2

English

Irish

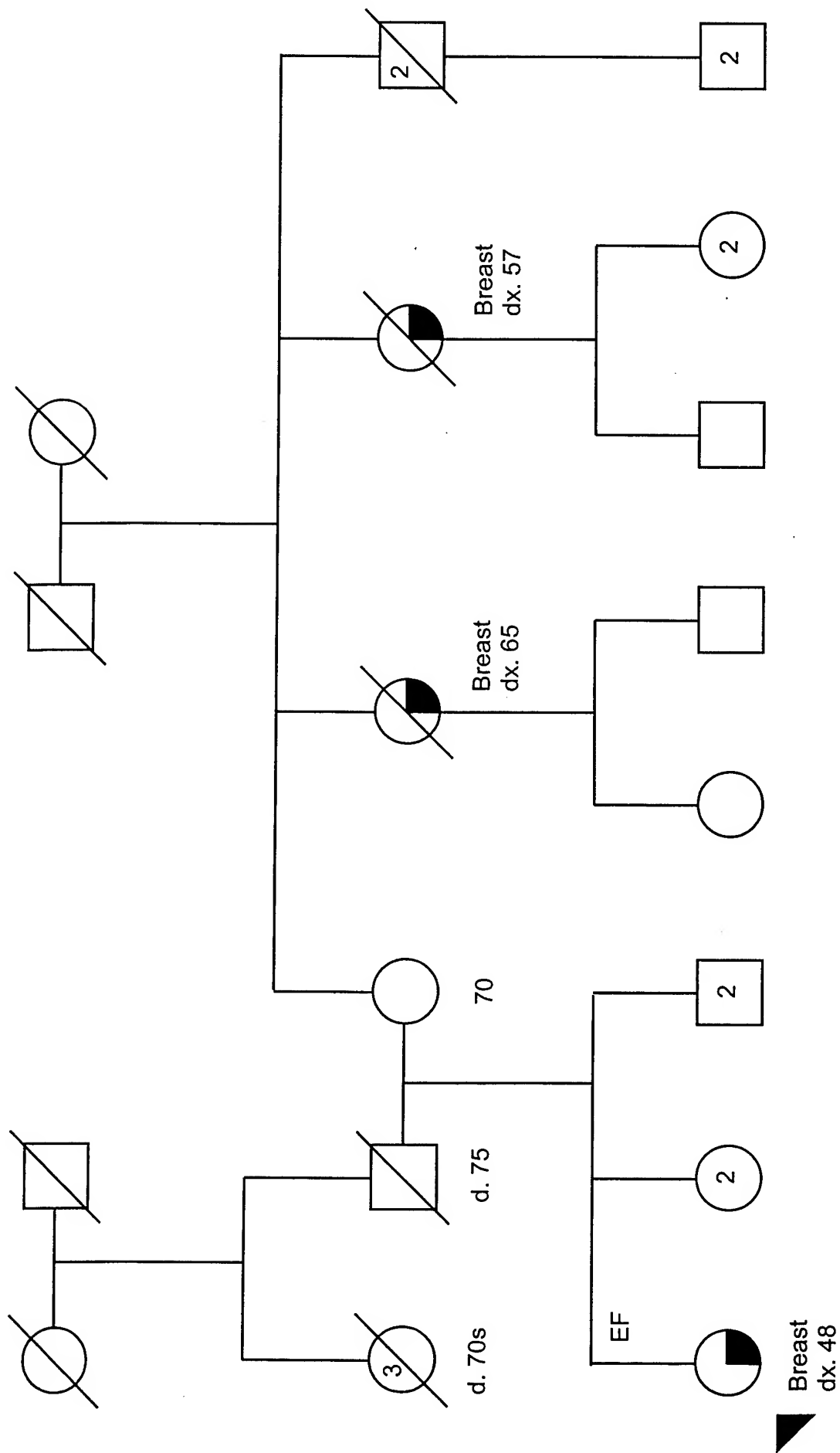


Figure 3

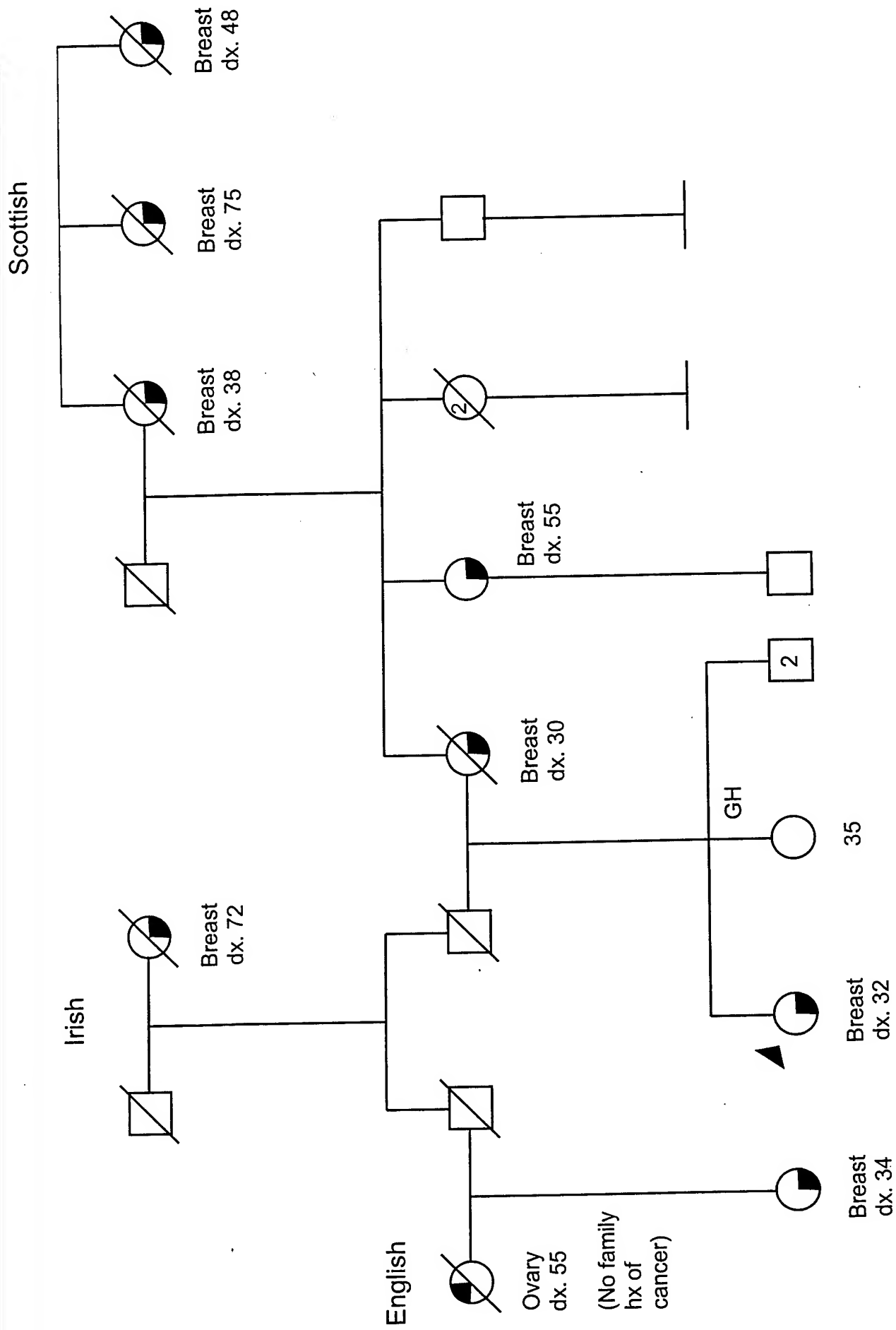


Figure 4

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GENETICS

AND

PUBLIC HEALTH

IN THE

21st CENTURY

Using Genetic Information to Improve Health and Prevent Disease

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2000

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19

Impact of genetic information and genetic counseling on public health

Judith L. Benkendorf, Beth N. Peshkin,
and Caryn Lerman

In this chapter we will review the evolution of the genetic counseling process as an integral part of genetic health and medical care. We will discuss the settings in which genetic counseling presently occurs and who provides these services. This discussion will include the role of genetic counseling as an adjunct to testing in preconception and prenatal care, as well as in general medicine. In addition, we will review literature on the impact of various genetic counseling and testing programs on patients' quality of life and health-related behaviors. We will conclude with a discussion of the current role of genetic counseling in public health and an examination of the advantages and disadvantages of a model that addresses and integrates the goals of both fields while maximizing the strengths of each.

Genetic Counseling

Definition and History

The term *genetic counseling* was introduced by Sheldon Reed in 1947 (1). Working at the University of Minnesota's Dight Institute, Reed found himself providing support and genetic information—often recurrence risk information—to an increasing number of families. Believing that the scope of this activity reached beyond genetic social work, he introduced the expression “genetic counseling.”

The roots of the contemporary genetic counseling movement can be traced to departments of medicine and pediatrics in academic centers, as physician and PhD medical geneticists evaluated individuals with mental retardation, birth defects, and conditions believed to be inherited. Their consultation

included: diagnostic workups; medical management; information about the etiology of a condition, including its modes of inheritance, and the risks for that condition occurring among family members or future offspring; and support for patients and their families. With the introduction of mid-trimester amniocentesis and sonography to geneticists' prenatal diagnostic tools, genetic counseling services were established in departments of obstetrics and gynecology. An overview of the current practice of prenatal genetic counseling can be found later in this chapter.

In 1969, Sarah Lawrence College, in Bronxville, New York established the first graduate program for the preparation of master's level genetic counselors. Graduates of that program, trained in the science of medical genetics and the art of counseling, went on to become full-fledged members of health care teams, responsible for serving as liaisons between medical geneticists, laboratories, and families. From this point forward, the term *genetic counseling* referred to both a distinct profession and to an activity performed by an array of genetics specialists. Throughout this chapter, "genetic counseling" will be used to refer to this broader activity.

The widely accepted definition, developed in 1975 by an ad hoc Committee on Genetic Counseling of the American Society of Human Genetics, describes the work of genetic counseling professionals.

Genetic counseling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to: 1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; 2) appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives; 3) understand the alternatives for dealing with the risk of recurrence; 4) choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision; and 5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder (2).

The values that distinguish genetic counseling from more traditional forms of medical consultation and counseling are spelled out in the Code of Ethics of the National Society of Genetic Counselors (NSGC) (3). The second section of the code describes the relationship of genetic counseling professionals with their clients and encourages them to strive to "respect clients' cultural traditions, circumstances, and feelings," and to "enable clients to make informed, independent decisions, free of coercion, by providing or illuminating necessary facts and clarifying alternative and anticipated consequences" (3). In the final section of this chapter, as we discuss the adaptation of current genetic counseling models to a public health model, we will examine the impli-

cations of the guidelines set forth in the NSGC Code of Ethics for the responsibilities that genetic counseling professionals have to society.

The Genetic Pedigree: A Personalized Risk-Assessment and Screening Tool

It is standard practice for genetics professionals to construct a genetic pedigree, or family tree, during encounters with patients seeking genetic services. During this process, a structured interview is used to gather information about the health histories of family members in multiple generations; standardized symbols (4) depict family relationships and the pattern of transmission of genetic conditions in the family. Accurate pedigrees provide the basis for assessing people's risks for both single-gene and multifactorial conditions and for making formal genetics referrals.

Patients who do not have genetic counseling at the time of prenatal diagnosis (or other genetic testing) miss the opportunity to have their pedigree analyzed by a genetics professional. In addition to their use in assessing reproductive risk factors (e.g., family history of mental retardation, birth defects, single gene disorders), pedigrees can provide a great deal of information about common adult-onset conditions. A number of these conditions may have a genetic basis, and in some cases it is possible to identify those individuals at highest risk and to modify personal risk by increased surveillance or by changes in lifestyle or health behaviors. Not only do pedigrees provide a basis for determining who should be offered genetic testing and surveillance and prevention opportunities, but they also allow for the identification of eligibility for genetic research studies. A carefully constructed and analyzed pedigree can sometimes even help allay patients' fears and save health care dollars by reducing the number of unnecessary genetic tests performed. It also can uncover critical information that can improve the accuracy of genetic counseling.

The multiple advantages of replacing conventional medical history-taking with the genetic pedigree-taking process, despite the labor-intensiveness of the latter, are listed in Table 19.1 (5).

Role of Genetic Counseling in Reproductive Health

Genetic testing provides prospective parents opportunities to obtain two distinct types of genetic information, each of which could influence their reproductive decisions. Information about the parents' carrier status for common autosomal recessive disorders can be obtained through heterozygote screening which is usually performed selectively on the basis of patients' ethnic backgrounds. Information about a developing fetus's health, well-being, and genetic status can be gleaned from prenatal screening tests such as sonography and

Table 19.1 Impact of the Genetic Pedigree on Medical Care

As a diagnostic and screening tool, the pedigree

1. Identifies genetic conditions in a family
2. Provides a basis for clinical diagnosis
3. Elucidates modes of inheritance
4. Allows for accurate genetic risk assessment and counseling
5. Documents complex family relationships pictorially
6. Identifies family members "at risk"
7. Is critical for genetic testing by linkage analysis
8. Facilitates referrals to genetics professionals and research protocols
9. Is easily stored and updated in the medical record
10. Promotes communication between medical team members.

maternal serum-marker screening, and from prenatal diagnostic procedures such as amniocentesis and chorionic villus sampling (CVS).

Prenatal Diagnosis Modalities

Maternal serum-marker screening is performed on a blood sample taken from a pregnant woman to identify those at increased risk of having a baby with certain birth defects, including spina bifida, anencephaly, Down syndrome, and trisomy 18. The patient's prenatal care provider usually educates the patient and elicits consent; the blood sample is then drawn during the 15th through 20th week of pregnancy. It is analyzed most commonly for concentrations of three chemicals found in women's blood during pregnancy: alpha-fetoprotein (AFP), beta human chorionic gonadotropin (hCG), and unconjugated estriol (uE3). Hence, this test is also referred to as a "triple screen." The concentrations of these three chemicals continue to change during pregnancy, but certain pregnancy complications and birth defects are known to produce specific changes, or patterns, in their concentrations. Maternal serum-marker screening is not diagnostic; it merely identifies women who are at increased statistical risk for having a child with certain birth defects. Women with abnormal triple screen results are referred for sonography, amniocentesis, and, often, genetic counseling.

A unique, statewide public health program for the dissemination, and subsequent follow-up, of maternal serum marker screening was established in California in 1986 (6). Administered and regulated by the California Department of Health Services, Genetic Disease Branch (GDB), the program is a private/public partnership that was initially authorized by the state legislature in 1985. By law, all pregnant women enrolled in prenatal care before 20 weeks' gestation must be provided a state-prepared patient education

brochure describing the risks, benefits, and limitations of screening; women then sign the program's consent/refusal form. Under the strict quality control of the state, the specimens are analyzed by one of eight regionalized private laboratories. Positive test results are electronically transmitted to 14 regional state-approved coordinators located at various publicly and privately funded genetics centers contracted by the state to provide follow-up. In addition, the patient's clinician is notified. Genetic counseling services and any indicated prenatal diagnoses are then offered at one of 29 prenatal diagnosis centers with 90 satellite sites, all meeting state criteria for counseling, ultrasound, amniocentesis, and laboratory services. There is a one-time only, all-inclusive fee to participants of \$115, which is billed to the patient or her insurance carrier. The state reports a steady increase in participation, from 41% of eligible women in 1986, to 63% of eligible women in 1994.

Although program officials claim that the "model has achieved its overall objective for providing universal access to low-cost, high-quality screening and follow-up" (6) the social risks of screening for the prevention of birth defects as a public health initiative cannot be ignored. Potentially, such programs run the risk that patients will not perceive the offering of these tests as an option they are free to decline, but rather as a recommendation to which they are expected to consent, even if they do not want to obtain the information to be learned. They may also feel obligated to act on abnormal results in a manner inconsistent with their values. Hence, the critical importance of the public education, genetic counseling, and multiculturally focused components of these programs cannot be overemphasized in order to assure their success in an environment that embraces individual patient autonomy. The burden on public health programs and officials may be even greater than those of private health service providers.

Sonography, also referred to as an "ultrasound examination," is a diagnostic imaging technique that uses ultra-frequency sound waves to visualize a developing fetus. Sonography is used routinely to date a pregnancy, determine the number of fetuses, and confirm the presence of a fetal heartbeat. Obstetricians and radiologists with special expertise in the use of sonography can assess fetal development and well-being and also determine the presence of major malformations or birth defects. Because sonography has no known medical risks to the mother or fetus, it is used widely, most commonly without much discussion about the benefits and risks of having the test. However, sonography can pose certain problems should parents begin learning information about their developing baby that they would rather not have known or are unprepared to handle.

Amniocentesis is a diagnostic prenatal test performed by a skilled obstetrician during the 15th through 18th week of pregnancy. The amniocentesis procedure involves using a needle, passed through a woman's abdomen into the uterus, to remove a small sample of the amniotic fluid in which the fetus is

developing. The amniotic fluid contains cells shed by the developing fetus; both the amniotic fluid and the fetal cells can be used to test for biochemical disorders and single-gene conditions for which a DNA-based test exists, and to analyze the fetus's chromosome constitution. The most common reasons for performing amniocentesis include an increased risk for chromosome abnormalities due to advancing maternal age (i.e., greater than 35 years at the time of delivery); a family history of a genetic disorder for which prenatal tests are available; and possible problems detected by an abnormal result on a sonogram or maternal serum-marker screen. Because amniocentesis carries a very small increased risk for miscarriage, it is offered only when there is a sound medical indication.

Chorionic villus sampling (CVS) involves removing a very small sample of the cells in the outer layer of the developing placenta during the 10th through the 12th week of pregnancy. These cells, known as chorionic villi, contain the same genetic information as do the cells of the fetus and therefore can be used to test for chromosome abnormalities and biochemical and single gene disorders. CVS does not, however, provide information about neural tube defects or other anatomic malformations. Because the risk for miscarriage associated with CVS is slightly higher than that associated with amniocentesis and because it is not as widely available, CVS is reserved primarily for those women who will be 35 years or older at the time of delivery and those with a significant family history of a genetic disorder for which prenatal testing is available. In these cases, CVS allows parents to obtain genetic information earlier in pregnancy, and this may make it somewhat easier (at least physically) for an abnormal pregnancy to be terminated.

Genetic Counseling for Prenatal Diagnosis

Both amniocentesis and CVS were introduced in research trials—primarily undertaken at academic medical centers—designed to evaluate their safety and efficacy (7–9). Under these conditions, genetic counseling was an integral component of the testing process (10). Beyond facilitating parental decision making, genetic counseling ensured informed parental consent by delineating the risks, benefits, and limitations of the procedures as described above. Genetics professionals explored how parents would use the information they might learn from prenatal diagnosis. If a genetic abnormality was discovered, follow-up counseling could be provided by the same genetics professional who already had an established relationship with the patient and her partner.

Because CVS continues to be offered primarily within genetics units (either in hospitals or medical centers) and a few free-standing genetics centers, genetic counseling prior to CVS remains fairly standard. Amniocentesis, in contrast, is being performed with increasing frequency in obstetricians' offices. The methods by which patients receive pretest information and counseling are highly variable, ranging from being given a pamphlet or having a brief dis-

cussion with their physician, to receiving more formal counseling by a board-certified genetics professional. In the former two situations, if a genetic abnormality is discovered via analysis of the amniotic fluid, the patient's physician will either provide further counseling or refer the patient to a genetics professional. Such patient encounters are often difficult for both counselors and patients because a helping relationship must be built at a time of crisis for the family; counselors may also find themselves providing genetics education to patients who have not fully understood the nuances of the genetic information they could learn from these tests.

If current trends continue to move prenatal testing from the tertiary centers to the community, or primary-care settings, and third-party payers are less inclined to reimburse for patient education, most patients seeking prenatal diagnosis will receive genetic counseling only if an abnormal test result occurs. Pre-amniocentesis and pre-CVS genetic counseling will be provided to the shrinking proportion of patients referred to medical centers or to genetics professionals for their procedures and to those seeking genetics services because of a family history of a genetic condition or an abnormal sonogram (e.g., those other than patients of advancing maternal age or with abnormal maternal serum marker screening results). Although many obstetricians have become quite proficient at performing the prenatal diagnostic procedures, far fewer are proficient at conducting pretest genetic counseling and eliciting informed consent, interpreting complex genetic test results, and providing support during decision making about whether to continue or terminate a pregnancy.

Models for Delivery of Heterozygote Screening

Heterozygote screening refers to voluntary blood tests, generally performed before or during the early part of pregnancy, to identify individuals who carry one copy of an altered gene for a recessive disorder, in which receiving two copies of the altered gene results in an individual affected with the disorder. In other words, if both members of a couple are found to be carriers of the same altered gene, each pregnancy will have a 25% risk to have a child affected with the disease. It is estimated that each person carries 5 to 12 altered genes for recessive conditions. The likelihood that a given individual and his or her partner carry the same recessive gene increases if they share a common ethnic background. In their "Guidelines for Perinatal Care," the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) state that "Certain autosomal recessive diseases are sufficiently common to warrant screening for heterozygosity. For example, such screening should be offered to those of Jewish ancestry to identify carriers of Tay-Sachs disease; to Blacks, to identify carriers of sickle cell anemia; and to individuals of Italian, Greek and Oriental descent to identify carriers of thalassemia" (11). The 1998 ACOG recommendation to add Canavan disease to the screening guidelines for Ashkenazi Jewish individuals (12) represents the first expansion to carrier screening protocols in over two decades. This trend is expected to

continue, driven by the proliferation of new genetic tests as an outgrowth of the Human Genome Project.

In the United States the vast majority of heterozygote screening is currently provided by professionals rendering prenatal care (obstetrician-gynecologists, nurse-midwives, and family physicians), either preconceptionally or at the time of the first prenatal visit. The amount of patient education provided beforehand is not standardized, but often involves no more than the dissemination of a patient education brochure. Referrals for formal genetic counseling are rarely made unless both members of a couple are identified as carriers of the same recessive gene (13). Historically, sickle cell and Tay-Sachs screening programs have offered some important lessons about the impact of carrier screening on public health and policy, and are discussed in Chapter 4. These are lessons that should still not be forgotten today.

In 1983, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research examined the sickle cell and Tay-Sachs screening models retrospectively and outlined the following parameters for heterozygote screening programs: (1) test results should be kept private and confidential; (2) decisions about screening should be made autonomously by the parents to ensure that screening is used for reproductive planning and not specifically to alter the gene pool; (3) pilot studies should be conducted to demonstrate that screening is valuable and can be conducted safely and effectively; (4) laboratory assays should have a high degree of sensitivity in the target population and be inexpensive enough to allow for cost-effective screening; (5) laboratory results should be reproducible; (6) the full range of prescreening and follow-up genetics education and counseling services should be available to the population being screened; and (7) equity of access to screening should be ensured (14). Given the nature of the health care delivery system in the United States, it seems unlikely that a national public health effort to provide heterozygote screening for reproductive risks will occur again; rather, such screening will likely continue to be provided under the purview of primary reproductive health care providers, with sensitivity to the parameters outlined in the President's commission report.

Role of Genetic Counseling in Adult-Onset Disorders

Common adult disorders such as heart disease, diabetes, certain types of mental illness and neurologic conditions, and many cancers have a genetic component that may be inferred from examination of the family history. However, as most of these conditions are multifactorial and only rarely are caused by mutations in a single gene, risk assessment is usually based on empirical data and pedigree analysis. Although genetic test results may provide more precise information for making risk estimates, including the determination of

Table 19.2 Characteristics of Monogenic Versus Complex Conditions of Adulthood

Parameter	Monogenic Conditions	Complex Conditions
Primary indication for genetic counseling/testing	At least one affected first-degree relative with distinct phenotype	Constellation of affected relatives in the same lineage
Goal of gene testing	Presymptomatic diagnosis	Identification of susceptibility
Gene penetrance	Usually very high	Highly variable
Phenotype	Somewhat consistent	Highly variable
Impact of environmental factors on phenotype	Usually minor	Potentially significant

those who are not at high risk, such testing is often not feasible or available. For some diseases, mutations in a single gene (monogenic diseases) appear to account for the majority of the cases. In these scenarios, options for testing and the approaches to counseling are quite different from those that exist for complex conditions, such as polygenic and multifactorial disorders (see Table 19.2). This section will highlight some monogenic and complex conditions of adulthood with particular attention to the utility of testing and the important issues that arise in the context of genetic counseling. A discussion of research on the outcomes of genetic testing for adult onset diseases can be found later in this chapter.

Monogenic Conditions

Monogenic conditions are genetic disorders that appears to involve only one gene. Following are two examples: familial adenomatous polyposis (FAP) and Huntington's disease (HD).

Familial Adenomatous Polyposis. An autosomal dominant condition affecting over 50,000 people in the United States (15), FAP is characterized by the development of hundreds of adenomatous colorectal polyps, which, if left untreated, invariably progress to cancer. The polyps are generally evident by the second or third decade of life but may also occur in early childhood. As more people live longer after being successfully treated for FAP (often by colectomy at a young age), the later manifestations of FAP may become apparent and cause significant morbidity. These later manifestations include gastric polyps and cancers of the thyroid and duodenum. Mutations of the APC gene are detectable in over 85% of patients with classic FAP (15). There is a compelling argument that people with FAP, especially those with an identifiable mutation, should inform their relatives about their risk and the availability of testing. Results of testing could then determine if intensive colon surveillance, which should commence in childhood, must be continued in carriers or eventually discontinued in noncarriers (16). Thus, genetic counseling and testing

may help individuals and families obtain important information that can assist in critical medical management decisions.

Huntington's Disease. This condition is caused by mutations in the IT-15 gene on chromosome 4p (17). If people with the altered gene live to old age, they are virtually certain to be affected by an inevitable progression of characteristic neurological and psychiatric symptoms culminating in death. It is estimated that approximately 30,000 Americans have HD and that another 150,000 are at risk for inheriting HD from a parent (18). At present, there is no proven intervention or treatment that can delay or prevent the natural progression of HD. As a result, people considering genetic testing for HD should be informed that if they do carry the IT-15 mutation, learning so will not help them to reduce their risk of developing HD nor will it necessarily have an impact on management of the disease. However, testing may be potentially beneficial for psychological reasons and may aid in reproductive decision making (19,20). The impact of test results on an asymptomatic individual, whether positive or negative, can be substantial, which is why extensive genetic counseling and psychological evaluations are critical (21).

Complex Conditions

Most conditions of adulthood are caused by a complex interplay of multiple genes acting in conjunction with environmental factors. This scenario makes risk assessment particularly challenging. People with one or two affected relatives may be counseled with the use of empirical data, although these data sets have inherent limitations. When pedigree analysis reveals a Mendelian or monogenic pattern of inheritance, genetic testing is more likely to be of value in risk assessment. However, interpretation of results can be complicated by the uninformative nature of some negative test results and the unknown role of modifying factors. The following examples illustrate these points.

Alzheimer's Disease. Alzheimer's disease (AD) is very prevalent, affecting over 4 million Americans, and resulting in more than 100,000 deaths each year (22). Sporadic and familial forms of AD have been noted, and three genes have been associated with early onset forms of AD (22). The 4 allele of the apolipoprotein E (*APOE*) gene has been observed in both sporadic and familial cases of AD and has been associated with as many as half of all AD cases (22). In addition, the gene exhibits a dose-dependent relationship with risk. As is the case with many other genes conferring disease susceptibility, gene penetrance (i.e., the likelihood that a carrier will develop the disease) is not absolute, and the gene expressivity with respect to age of onset and severity is variable. Unlike HD, however, AD may be mitigated by certain medications, although the effectiveness of interventions with these medications is yet unproven (23-25). Thus, the psychological impact of learning that one is susceptible to AD may be less severe given that penetrance is unclear and there are proposed prevention and treatment options.

The strongest arguments supporting *APOE* genotyping relate to its potential usefulness for diagnostic purposes and for targeting individuals who may be good candidates for therapeutic interventions (26,27). Such testing is very controversial and has not been endorsed (26). Nevertheless, there may be valid reasons for offering genetic testing, but it should be offered only after careful discussion of the potential risks as well as the benefits of such testing, especially since positive test results could have negative psychosocial consequences for the person tested, as well as implications for his or her relatives.

Breast Cancer. Breast cancer, the most common malignancy affecting women in the United States (28), is another prevalent disease that can be inherited. Five percent to 10% of breast cancer cases have been attributed to alterations in a single susceptibility gene such as BRCA1 or BRCA2 (29); however, other less common genes also contribute to hereditary breast cancer, such as *p53*, *ATM*, and other unidentified genes (30). Mutations in the two major "cancer genes," BRCA1 and BRCA2, confer dramatically increased risks for breast cancer (36%-85%) and ovarian cancer (15%-60%), with a significant amount of the risk occurring premenopausally (31-33). In the absence of long-term outcome data or controlled clinical trials of interventions, there are no standard recommendations about ways to reduce these risks, and optimal methods of early detection have not been established; however, increased surveillance and discussion of prophylactic surgery have both been suggested as options for BRCA1/2 carriers (34-36). Heightened screening can be an effective early detection measure for at least some high-risk women. As the effects of reproductive and environmental factors, hormone use, and modifier genes become better characterized, clinicians may be able to tailor risk estimates for specific patients and provide additional options for risk reduction. Counselors should address the uncertainty associated with interpreting test results including issues related to the variable expression and incomplete penetrance of these genes and also discuss the uncertainty of efficacy of measures to reduce risk.

Although BRCA1 and BRCA2 mutations do not appear to be implicated strongly in the development of sporadic breast cancers, an improved understanding of the function of these genes and the development of new screening and prevention methods for carriers may translate into more effective prevention and treatment options for the population at large, thus dramatically affecting public health considerations. Eventually, women in the general population may also benefit from obtaining risk profiles based on genotyping of common low-penetrance genes such as GST and CYP17 (37,38) in combination with an assessment of environmental risk factors. It may then become possible to target interventions such as those involving chemopreventive agents to certain subsets of women on the basis of more precise risk estimates. This approach to identifying women at high risk for breast cancer was used in

the NASBP-P1 Breast Cancer Prevention Trial of tamoxifen (39). In this trial, eligible high-risk women were identified on the basis of risk calculations derived from the Gail model, which uses family history, personal breast biopsy history, and reproductive factors to determine level of risk. The trial data indicate that the incidence of breast cancer was 49% lower among women who received tamoxifen. A substudy will determine what proportion of participants were BRCA1/2 carriers and whether the effects of tamoxifen in this population were comparable to the results as a whole. It is important to note that other studies of tamoxifen use by women at high risk for breast cancer did not show a protective effect (40,41).

Counseling Issues

Identifying individuals and families who are most likely to benefit from genetic testing and counseling can be a challenge. The clinician must consider several factors: the likelihood that a test will be informative; the degree of uncertainty associated with interpretation of results; the impact of test results on medical management; the implications of test results for family members; and the potential risks of testing, including insurance discrimination and psychological sequelae. For many monogenic conditions, mutations in the causative genes tend to be highly penetrant, meaning that carriers almost always develop the condition. Although steps may be taken to mitigate the disease course, the disorders are usually not entirely preventable. The interpretation of genetic test results for monogenic conditions can be relatively straightforward and can lead to an improved medical management plan for the individual tested. Because monogenic conditions have low rates of sporadic occurrence, true negative results (i.e., obtained after a mutation is identified in a family) indicate that the person tested is at very low risk for developing the disorder. Thus, the psychological relief from knowing one's genetic status can be substantial.

Genetic counseling and testing for complex disorders requires a broader discussion of the limitations of pedigree analysis and the uncertainties associated with test-result interpretation. Medical management for these types of conditions can be more varied and have differing or even an unknown level of efficacy. Because multifactorial conditions are common, people who test negative for a mutation in their family still need to be aware of general population risks and follow screening guidelines, when applicable.

Genetic Counseling Process

The issues described herein are of sufficient complexity that patients who have suggestive family histories should consider genetic counseling. Where genetic testing is an option, genetic counseling is critical both before and after testing. Counseling for adult-onset disorders is a departure from "traditional" genetic

counseling in that the emphasis is not on reproductive risks, but on issues related to an individual's own disease susceptibility and preventive options (42). Typically, an initial genetic counseling session consists of the following: (1) a compilation of a detailed, minimum three-generation pedigree, with documentation of diagnoses where possible; (2) a review of the patient's medical history, with added attention to lifestyle habits, exposures, and current medical management; (3) a risk assessment based on pedigree analysis and empiric data, where applicable, including notification of anyone else who might be at increased risk for the condition in question; (4) a review of the potential benefits, limitations, and risks of genetic testing; (5) a discussion of medical management options, including uncertainties about efficacy; (6) consideration of the patient's and his or her family's coping mechanisms and their likely emotional response to risk assessment or genetic-testing results; and (7) provision of referrals and follow-up plan (43).

If an individual chooses to undergo genetic testing, post-test counseling is critical. In many cases, counseling at this time may focus less on the medical implications of the test results and more on the psychological integration of risk notification and issues in family communication. Thus, genetic testing and counseling should remain intrinsically linked. Such counseling maximizes the likelihood that people will better understand the meaning and interpretation of their test results and will obtain the greatest benefit from testing while minimizing the potential for adverse consequences.

Because of the nature of the conditions discussed in this chapter, individuals who might benefit from genetic counseling are most likely to be identified by physicians in disciplines such as internal medicine/primary care, gynecology, and oncology. These providers need to elicit and recognize suggestive family histories and to make referrals for genetic counseling when needed. Still today, much of the genetic counseling for adult-onset conditions is provided by genetic specialists who often work in university hospitals or tertiary-care centers. In fact, much of the early presymptomatic genetic testing occurs within the context of research protocols, which include institutional review board approval, genetic education and counseling, and informed consent. The comprehensive model of cancer-risk counseling may be useful in developing testing protocols for other conditions because it involves both pre- and post-test counseling, integrates epidemiologic data into risk assessment, and is often performed in a multidisciplinary setting (43,44). However, as new genetic technologies move into the primary-care arena, physicians in those settings may become increasingly responsible for providing pre-test education and counseling (45). In this situation, patients may be referred to a genetics specialist only in the event of a positive, uninterpretable or uninformative test result, an unusual family history, or other complex or unanticipated outcomes.

Implications

In examining the leading medical causes of death in the United States in 1997 (28), over half the conditions may have arisen from an inherited predisposition. Heart disease, cancer, and diabetes all develop as a result of combinations of exogenous and genetic factors. Genetic testing may have broad public health implications in that it may allow improved identification of those at increased risk for these and other illnesses; however, the full potential benefits of such testing are not likely to be obtained without concomitant genetic education and counseling (45), the realization of interventions to reduce risk, and widespread access to these services. A model that will likely develop to deal with common chronic adult-onset conditions will include risk assessment and management plans based upon genetic and environmental variables that will need to be tailored to each individual (46). Data obtained from epidemiologic studies and public health research will likely be used to develop the models. At this time, it is vital to educate people about the importance of knowing one's own family history, adhering to age-appropriate screening, and adopting healthy lifestyles and behaviors.

Outcomes of Genetic Counseling

In this section we review both the literature on outcomes of genetic testing and individual factors that may modify outcomes in different population groups.

Reproductive Intentions and Behaviors

Although change in reproductive behavior is not considered a primary outcome of genetic testing and counseling, preliminary data suggest that such testing may have an impact on reproductive choices. For disorders that are not preventable or successfully treated, carrier testing and subsequent prenatal diagnosis may provide an option for those who wish to have children and avoid having an affected child. In a screening program to detect carriers for hemoglobinopathies, Rowley et al. (47) reported that 55% of pregnant women identified as carriers suggested testing to their partners; however, only one-half of partners were actually tested. Among pregnant couples found to be at one-in-four risk to have an affected child, 47% accepted prenatal testing; however, the pregnancies were continued in all but one case (in which the woman was herself affected).

Similar outcomes were observed in screening programs for cystic fibrosis (CF). In one CF screening program in the United Kingdom, 57 of 100 identified carriers suggested testing to their partners, and 87% of those 57 partners were subsequently tested (48). Of those who participated in genetic counseling, 36% said that they would consider terminating an affected pregnancy,

whereas 20% of those not receiving genetic counseling said they would. Similarly, Loader and colleagues (49) found that avoiding having an affected child was a primary motivation for accepting CF screening in a primary-care setting. People who agreed to undergo CF screening were more likely to report prior to screening that they would consider terminating a pregnancy if the fetus was affected. However, data on actual reproductive decisions by carrier couples are not available.

In a review of the literature on predictive testing programs for Huntington's disease, researchers indicated that childbearing decisions were reported as a primary motivation for testing by 20% to 60% of study participants (50). In another study, three-fourths of participants reported that they would terminate a pregnancy if the fetus was found to have the HD gene (51). As yet, however, data on actual use and the outcomes of prenatal testing for HD have not been reported.

Behavior Modification and Personal Risk Reduction

Even though no interventions have been proven to reduce risk in carriers of BRCA1 and BRCA2 mutations, data from surveys of individuals at risk have suggested that behavior modification is a primary motivation for genetic testing. For example, in a study of first-degree relatives of breast cancer patients, 80% of respondents reported that obtaining more frequent screening tests was an important motivation for pursuing BRCA1 testing (52). In a study of hereditary breast-ovarian cancer families, 93% of women reported that they wished to obtain genetic testing in order to increase the frequency of cancer screening, and 85% were motivated by the desire to obtain information to make decisions about surgical prevention (53).

Although outcome data from genetic testing programs for most complex diseases are not yet available, preliminary data on genetic testing for cancer-predisposing genes suggest that these reported motivations may not translate into actual behavior changes (53). Among those aged 35 and older who were due for an annual mammogram, only 61% had a mammogram within 6 months after testing. Furthermore, only 6% adhered to the recommendations for biannual ovarian cancer screening tests. Such low percentages of women who followed recommended cancer screening practices following BRCA1/2 testing may be attributable at least in part to the limited data available on the efficacy of cancer screening among younger women at increased risk for cancer. However, even if efficacy was proven, some women still might not adhere to recommendations.

Reports documenting a lack of behavioral change among people found to be at genetic risk for lung cancer are particularly striking (54,55). Smokers who received genetic test results indicating a two- to four-fold increased risk for lung cancer associated with smoking reported short-term increases in their motivation to quit smoking and made more attempts to quit. However, they

were no more likely to quit smoking than were smokers receiving standard counseling without genetic test results. Moreover, smokers found to be at increased risk reported short-term increases in depression symptoms; however, these symptoms returned to baseline 12 months later. Thus, even when there is an unequivocally beneficial action for reducing risk, genetic testing may not lead to the hoped for changes in health practices.

Quality of Life

Despite the potential medical benefits of genetic testing, there are concerns that disclosure of genetic information may create a significant emotional burden. Research on the psychological effects of prenatal and carrier testing was reviewed recently by Croyle and Lerman (56). This review, and a review of studies focused on HD (50), concluded that testing may lead to short-term increases in emotional distress but that most participants suffer no significant longer-term effects on their quality of life.

More recent reports extend these findings to other adult-onset diseases. For example, in the study of hereditary breast-ovarian cancer families noted above, people found to carry mutations in the BRCA1 or BRCA2 genes exhibited little change in depression symptoms or functional health status from their pre-test assessment to 6 months after the test (57). Prior to testing, their levels of distress were not different from those in the general population. Noncarriers of mutations experienced a significant improvement in mood during the month following testing, but their scores on this measure returned to baseline levels 6 months later. People who declined to be tested reported the highest levels of distress, but these levels were not significantly different from those of carriers or noncarriers; all scores before and after testing were well within the normal ranges. Interestingly, these results mirror the findings of Wiggins and colleagues (58), who studied people offered predictive testing for HD.

Although individuals found to carry disease-predisposing genes may not experience significant adverse psychological effects, there is evidence that testing may have more subtle influences on their quality of life. For example, Croyle and colleagues found evidence of short-term increases (1 to 2 weeks) in cancer-related distress among women identified as BRCA1 carriers who had not had a prior diagnosis of cancer or preventive surgery (59). Marteau and colleagues studied emotional responses following carrier testing for CF (60). Although they found that clinical levels of anxiety were not observed during the 3-year follow-up period, carriers and noncarriers differed significantly in more subtle cognitive and emotional responses (e.g., having troubling thoughts about the test results). Similarly, Tibben and colleagues (61) found that carriers of HD gene mutations experienced a variety of stress symptoms involving intrusive thoughts and avoidance of HD-related situations. However, they suggested that this pattern reflects a healthy coping response required to process

the significance of subjects' test results. In general, the partners of carriers showed patterns of stress symptoms similar to those of tested individuals.

Individual Differences

Observing the lack of significant adverse psychological effects that genetic testing had on patients' overall quality of life, researchers have sought to determine whether particular subgroups of patients may be more psychologically vulnerable. A recent report found that precounseling levels of cancer-related stress may be a useful predictor of quality-of-life outcomes among individuals undergoing BRCA1/2 testing (57). However, contrary to expectations, people with high precounseling distress levels who declined to be tested were at greatest risk for subsequent psychological morbidity. A post hoc analysis indicated that this subgroup of patients had strong motivations to be tested yet were concerned about their ability to cope with the information and had some fear of discrimination.

In the HD testing arena, research has also begun to identify subgroups of patients who may be more vulnerable to the negative emotional effects of genetic information. Similar to the study of hereditary breast and ovarian cancer families noted above, Tibben et al. found that precounseling levels of HD-related distress predicted poorer psychological adjustment. However, in this study, the carriers and not the decliners, were more prone to adverse effects (62). In another prospective study of HD testing, mutation carriers who were closer in age to the estimated onset of HD in their family were significantly more distressed than were other carriers (63).

Other studies have focused on sociodemographic factors that might influence responses to genetic information. In their study of HD testing, Codori et al. found that marital status modified the psychological impact of testing (63). However, contrary to predictions, married carriers of HD mutations were found to be less well adjusted than were unmarried carriers. Among people tested for CF, women were found to respond more positively than men when informed that they were noncarriers and less positively when informed that they were carriers (60). Investigators suggest that these differences may be attributable to different appraisals of threats to reproduction among men and women.

In a randomized trial, ethnic differences were observed in the responses of women with a family history of breast cancer to two alternate BRCA1 pre-test education strategies: a standard education model and an education plus counseling model (64). Among black women, those who received education plus counseling were more likely to plan to be tested and to provide a blood sample for genetic testing than were those who received education only. They were also marginally more likely to report cancer-specific distress. Among white women, there were no differential effects of the interventions on these outcomes.

Other studies suggest that people also differ in their preferences for providers of genetic counseling. For example, in a study of healthy women with a strong family history of breast cancer, 42% preferred that pre-test education for BRCA1/2 testing be delivered by a genetic counselor, whereas 22% preferred an oncologist (65). For post-test counseling, 38% preferred an oncologist, while only 20% preferred a genetic counselor. However, women who desired supportive counseling during this session were significantly more likely to prefer a genetic counselor to an oncologist.

These studies provide important insights needed to begin to understand patients' preferences for different modes of genetic counseling and to identify patients who may be more psychologically vulnerable to the effects of genetic testing. The results of such research can be used to develop counseling approaches that can be tailored to an individual's informational and psychological needs and sociodemographic background.

The Future of Genetic Counseling and Public Health

Can the current genetic counseling model be applied to a population-based, public health approach to genetic screening and predisposition testing? The present-day genetic counseling model focuses on helping individuals and their families make informed, autonomous decisions rather than on motivating individuals to change their health behaviors to improve the health of society. Lessons learned from counseling individuals and families may be helpful in developing genetic testing for subsets of the population deemed to be at risk. Experiences with sickle cell and Tay-Sachs screening should have sensitized both health professionals and consumers to social issues that can arise when a specific racial or ethnic group is targeted for genetic screening and research. For example, concerns about stigmatization and discrimination associated with predisposition testing resurfaced recently when investigators revealed not only specific genetic mutations in BRCA1 and BRCA2 in the Ashkenazi Jewish community (66), but also specific genetic mutations for colon cancer and deafness in the same population.

Genetics professionals are committed to participating in activities that promote the well-being of individuals and society, as delineated in Section IV of the Code of Ethics of the National Society of Genetic Counselors (3). This includes keeping abreast of societal developments that may endanger the physical and psychological health of individuals, serving as sources of reliable information for policymakers and public officials, and keeping the public informed and educated about the impact on society of new technological and scientific advances. It is here that partnerships between genetics and public health professionals the begin, with the goal of improving the health of society without losing sight of the needs and experiences of individual patients and

Table 19.3 Board-Certified Genetics Professionals as of 9/99*

Genetics Specialty	Number of Diplomates with Certificates
Genetic counselors	1410
M.D. clinical geneticists	1006
Ph.D. medical geneticists	150
Clinical cytogeneticists	522
Clinical biochemical geneticists	180
Clinical biochemical/molecular geneticists (combined exam given in 1990 only)	49
Clinical molecular geneticists	284

* This table represents 3601 certificates, held by 3269 individuals.

(Information provided by Sharon Robinson, Administrator to the American Board of Medical Genetics and the American Board of Genetic Counseling; personal communication).

their families. The challenge of the new millennium will be for genetics professionals to maintain a balance between their duties to patients and families and their commitment to addressing and advancing public health interests. The addition of public health professionals to the genetics team and the addition of genetics professionals to the public health team is therefore critical to fulfilling these goals and responding to the profound limits of our nation's pool of genetics professionals, as illustrated in Table 19.3.

Public Health Professionals and Genetics Professionals: A Critical Partnership

Genetics services will increasingly become an integral component of health care, especially as genetic risk factors become better understood and interventions to reduce risk become available. Public health professionals will provide leadership in designing programs that target specific populations and assure that these programs are readily accessible to all segments of society, including minority and underserved groups.

Public health professionals can have a role in assuring that genetics education is incorporated into all levels of public and professional education. They will also be pivotal to the development of general and specific education materials regarding the risks, benefits, and limitations of genetic tests and interventions to reduce risk. These materials might take the form of printed media, interactive videos, CD-ROMs, and even public service announcements that will supplement the activities of genetics professionals in this realm, and make this information more accessible than it is today. It will be vital for these genetics educational materials to provide more than the facts. They should also challenge the public to engage in values clarification strategies that would allow them to think about whether they would consider genetic testing and assess how they might personally use the information gleaned from genetic tests.

Just as important is the growing need for public health professionals to work with the genetics community in responding to new and rapid scientific breakthroughs that can engender a great deal of public and professional misinterpretation and misunderstanding. As information about genetic advances and new genetic tests becomes available to the public through the media and the Internet, such publicity is likely to generate more widespread interest in genetic counseling and testing. Thus, public health professionals must be equipped to respond to new advances, and subsequent public reactions, by specifically targeting education programs to populations for whom genetic counseling and testing may not be appropriate, and the number of genetics specialists too constrained to address and allay each individual's concerns and fears.

As genetics permeates all medical and health care, public health professionals will be called upon to serve as critical links for case finding, referral, and follow-up. This approach will have the power to combine the skills and expertise of the genetics specialists, especially in working with complicated family situations, genealogies, and very rare conditions, with the long-standing relationship among public health professionals, individuals, and society.

Finally, because rapid advances in genetics are expected to continue into the foreseeable future and the time from gene discovery to test development and clinical application will continue to become more compressed, ongoing professional education of the existing workforce is just as critical as the training of new professionals and informing the public. Genetics and public health professionals will share roles as consultants and partners in both public and professional education, with the ultimate goals of optimizing health care and the appropriate utilization of services. Such educational efforts will help ensure that individuals considering genetic testing will have an opportunity to make informed decisions and will be less likely to experience adverse or unanticipated consequences as a result of those decisions.

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Ed. GN Hortobagyi + D. Khayat
Progress in Anti-Cancer Chemotherapy
Paris, France Springer-Verlag, 1999

Hereditary Breast Cancer: an Overview

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Introduction

It is estimated that hereditary breast cancer accounts for up to 10% of all cases of breast cancer [1]. Thus, of the 180,000 cases of breast cancer diagnosed yearly, up to 18,000 may be due to an inherited predisposition to this disease. To date, several genes have been identified that account for different hereditary breast cancer syndromes. BRCA1 and BRCA2 mutations are thought to account for the majority of inherited breast cancer. Although less frequent, hereditary breast cancer may be a feature of Li-Fraumeni and Cowden syndrome and may also occur in Ataxia Telangiectasia heterozygotes. In addition, it is likely that other rare, as yet unidentified, genes exist.

This chapter will provide an overview of the major genes responsible for hereditary breast cancer and will focus on the following aspects of the BRCA1 and BRCA2 genes: 1) clinical features of individuals and families with a mutation in one of these genes; 2) the process of genetic testing including a review of the benefits, limitations and risks of such testing; 3) interpretation of genetic test results; and 4) management options for individuals who are found to have a mutation.

BRCA1 AND BRCA2

BRCA1 was localized to chromosome 17q21 in 1990 and identified in 1994 [2]. It extends over approximately 100,000 base pairs of DNA, encodes a very large protein of 1,863 amino acids, and is believed to function as a tumor suppressor gene. Mutations are inherited in an autosomal dominant fashion. BRCA2 was identified more recently, in December 1995 [3]. Like BRCA1, mutations are inherited in an autosomal dominant fashion, and it too is believed to be a tumor suppressor gene. It has 11,385 nucleotides and encodes a protein of 3,418 amino acids. However, the exact mechanisms of action of BRCA1 and BRCA2 remain unclear. The normal BRCA1 gene has been shown to suppress the growth

of ovarian and breast cancer cell lines [4]. Recent studies have suggested that BRCA1 and BRCA2 may play a role in transcription and DNA repair [5, 6].

It is not surprising, given the large size of both BRCA1 and BRCA2, that multiple disease-conferring mutations have been identified, many of them unique to individual families. To date, over 400 BRCA1 and BRCA2 mutations that are scattered throughout the gene have been documented [7]. Some of these mutations have been found to occur more frequently, particularly in certain ethnic groups. For example, two BRCA1 mutations, 185delAG and 5382insC, and one BRCA2 mutation, 6174delT, have been noted with increased frequency in individuals of Ashkenazi Jewish descent [8]. In addition, numerous BRCA1 and BRCA2 benign polymorphisms and variants of unknown significance have been identified [7].

Clinical Features of Hereditary Breast Cancer

The majority of identified cases of hereditary breast cancer appears to be associated with mutations in BRCA1 and BRCA2. Cancer risks conferred by BRCA1 and BRCA2 mutations are derived largely from highly selected families in which multiple women have developed early onset breast and ovarian cancer [9, 10]. Data from individuals with less striking family histories are beginning to emerge and suggest that on average, cancer risks are lower than those observed in the highest risk families [8]. Thus, while no single number can quantify precise cancer risks for an individual who tests positive, the risks should be interpreted within the context of a specific medical and family history. Information about risks associated with particular BRCA1 or BRCA2 mutations is not yet available, but ranges of cumulative risk estimates are summarized below (see Table 1).

BRCA1 and BRCA2

Cancer Risks

Women who inherit a BRCA1 mutation have a significantly elevated risk of developing both early onset breast and ovarian cancer. The lifetime risk of breast cancer in mutation carriers is estimated to range between 55-85%, with over 50% of these women being diagnosed by age 50 [8-10]. In addition, by age 70, 15-60% of BRCA1 carriers will have devel-

Table 1. Estimated cancer risks associated with BRCA1 and BRCA2 mutations*

Type of Cancer	Estimated Lifetime Risk in BRCA1 Mutation Carriers [8-12]	Estimated Lifetime Risk in BRCA2 Mutation Carriers [3, 8, 13-17, 41]	Lifetime Risk in General Population
Breast cancer (female)	55% - 85%	55% - 85%	13%
2 nd Breast cancer (contralateral)	Up to 65%	Probably similar to BRCA1 risks	Up to 1% a year (leveling off at up to 25%)
Ovarian cancer	15% - 60%	15% - 27%	1.4%
Ovarian cancer after breast cancer	Up to 30%-55%	Comparable to BRCA1 risks	2-3% (approximately twice the average risk)
Colon cancer	Possible relative risk of 4	Possible increased risk	Approximately 6%
Prostate cancer	Increased risk, possibly up to a relative risk of 3	Probable increased risk	At least 10% but risk is difficult to quantify due in part to the presence of clinically undetectable cancers
Breast cancer (male)	A few reported cases	Approximately 6%	Extremely rare
Pancreatic cancer	Not increased	Associations noted	Rare

Note: These risks are cumulative and are not mutation-specific. In general, early ages of onset have been associated primarily with female breast cancer and ovarian cancer. However, there are some reports of early onset pancreatic cancer associated with BRCA2 alterations. Relative risks, such as those associated with prostate and colon cancer in BRCA1 carriers, are not directly translatable to absolute risks. It is also important to note that general population risks include some patients with hereditary cancer. All risks must be evaluated in the context of the patient's medical and family history.

*Modified from [42]

oped ovarian cancer [8, 9]. In the general population, the risk of ovarian cancer is between 1–2%. In addition, mutation carriers with a prior history of breast or ovarian cancer appear to have an increased risk of developing a second malignancy. For example, the risk of contralateral breast cancer for mutation carriers who have already had a diagnosis of breast cancer has been estimated to be up to 65% by age 70 [10]. In comparison, for patients with sporadic breast cancer, the risk of contralateral breast cancer is thought to be 0.5–1% annually [18]. Little information exists on the risk of ipsilateral breast cancer recurrence in BRCA1 carriers who undergo breast conserving surgery. However, given the high rate of contralateral breast cancer in this population, the rate of in-breast recurrence in mutation carriers appears to be elevated also [17]. In addition, the risk of ovarian cancer after a diagnosis of breast cancer is elevated up to 44% by age 70 [10]. For women in the general breast cancer population, this risk is about 3%. In male mutation carriers, prostate cancer has been noted with increased frequency [8,10], although the absolute risk compared to the general population is not clear. There is some controversy about whether colon cancer is associated with BRCA1 mutations [8,10], and it is expected further studies will clarify this issue. When observed in mutation carriers, both prostate and colorectal cancer appear to have the same age distribution as is seen in the general population [10].

BRCA2 mutations are associated with a markedly elevated risk of breast cancer in women and in men. Whereas the risk of breast cancer in women has been estimated to vary between 55% and 85% [8,16], the risk of male breast cancer in BRCA2 mutation carriers is estimated to be about 6% [13]. However, in the general population, male breast cancer is extremely rare, with only 1600 cases of this disease diagnosed yearly in the United States [19]. Although BRCA2 is not as strongly associated with ovarian cancer as is BRCA1, the risk in mutation carriers is still elevated above that seen in the general population and the lifetime risk is estimated to be between 15–27% [8, 16]. Little information exists on BRCA2 carriers' risk of developing a second malignancy (e.g. contralateral breast cancer or ovarian cancer after a diagnosis of breast cancer), though these risks appear to be elevated also [17, 41]. Prostate cancer, though not diagnosed at an early age, also seems to be associated with BRCA2 alterations [8]. In addition, some studies have reported an increased frequency of pancreatic cancer [15, 20].

Cancer Prognosis

Recent studies have indicated that the breast tumors seen in BRCA1 and BRCA2 carriers appear histopathologically more "aggressive" than those observed in the general breast cancer patient population. These tumors have a higher histologic grade, are more frequently aneuploid, and have a higher S-phase fraction than tumors seen in women with sporadic breast cancer [21]. Despite this finding, some studies in BRCA1 carriers have shown the same or better prognosis than what is noted in the general breast cancer patient population when matched for age-at diagnosis [22] and stratified for stage of disease [21]. A more recent study however, suggested that the breast and ovarian cancer prognosis in BRCA1 carriers was the same or worse than that for an age- and stage-matched control group [23]. The BRCA2 breast cancer phenotype appears to be more heterogeneous than what is noted for BRCA1, and for BRCA2 carriers the breast cancer prognosis may be worse [21].

It is important to stress that the information on the prognosis of tumors in BRCA1 and BRCA2 carriers is derived from small studies and is therefore limited. In addition, it is possible that ascertainment and screening biases may have influenced the results obtained in these studies. Therefore, before integrating this information into clinical practice, it will be necessary to conduct larger studies to validate the findings of these reports.

Cancer Risk Modifiers

Investigators have begun to examine the impact of environmental factors and gene-gene interactions on the cancer risks of mutation carriers. In a study of 333 BRCA1 carriers from 28 different hereditary breast-ovarian families, Narod et al. [24] found that the risk of breast cancer was increased in carriers who underwent early menarche (relative risk 1.57 for menarche <12) and those who had had fewer than three live births (relative risk 2.04) when compared with carriers with an otherwise similar history. It was also observed that the risk of ovarian cancer was higher with increasing parity, but the risk was lower the older a woman was at last live birth [24]. With respect to oral contraceptives (OCs), a recent study of 50 young Ashkenazi Jewish breast cancer patients suggested that long term OCP use (i.e. > 48 months), particularly before a first full-term pregnancy, was associated with higher breast cancer risks in BRCA1/2 mutation carriers versus non-carriers [25]. That study did not determine whether OCP use decreases the risk of ovarian cancer in mutation

carriers; however, a recent case-control study revealed that six or more years of OCP use was associated with a 60% decrease in ovarian cancer risk in BRCA1/2 mutation carriers [26]. It is also possible that modifier genes may affect gene penetrance. For example, one group found that the risk of ovarian cancer in BRCA1 carriers with one or two rare *HRAS* alleles was about two times greater than noncarriers with common alleles [27].

The studies described in this section are based on relatively small sample sizes; therefore, these results will need to be validated in larger series. If the findings are substantiated, then it may be possible to determine more specifically an individual carrier's cancer risks and to devise strategies to minimize these risks.

Li-Fraumeni Syndrome

Although less frequent, breast cancer may be a feature of other hereditary diseases or syndromes which together probably account for fewer than 1% of all breast cancers. Among the most recognized of these is the Li-Fraumeni cancer syndrome—an autosomal dominantly inherited condition characterized by sarcomas, brain tumors, early onset breast cancers (often diagnosed < 30), leukemias, and adrenocortical cancer [28]. For individuals at risk, it is estimated that up to 50% will develop some form of cancer by age 30, and over 90% will develop cancer by age 70. Mutations in the p53 gene have been associated with Li-Fraumeni syndrome, and predictive testing may be available if a p53 mutation is identified in the family.

Ataxia Telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive syndrome characterized by cerebellar degeneration, immunodeficiency, telangiectasias, and predisposition to both solid tumors and hematologic malignancies. AT may occur in as many as 1/40,000 live births, and has an estimated carrier frequency of 1% [29]. DNA testing is now available for the gene implicated, known as ATM, which is located on chromosome 11q [30]. Although it has been suggested that over 8% of breast cancer patients in the United States may be carriers of the ATM gene and have an estimated relative risk of 4 compared to noncarriers for the development of breast cancer [31], others have refuted the idea that such carriers face an increased risk for early onset breast cancer [29]. Some concern has also been raised that breast cancer susceptibility in female heterozygotes may

be increased by exposure to ionizing radiation. It is hoped that large scale population studies will address this issue further.

Cowden Disease

Cowden disease is a rare autosomal dominant familial cancer syndrome that predisposes women to a high risk of breast cancer and an elevated risk of thyroid cancer. Hamartomas of the oral mucosa, such as multiple oral papillomas, are pathognomonic. Some estimates suggest that breast cancer may affect 20–30% of females with Cowden disease, often at an early age, and that there may be a higher than average incidence of bilateral cancer [32]. The gene for Cowden disease has been localized to chromosome 10q and clinical DNA-based testing may soon be possible [33].

Identification of High Risk Families

The clinical features suggestive of hereditary breast and ovarian cancer due to BRCA1 or BRCA2 mutations include the occurrence of breast and/or ovarian cancer, especially when noted in two or more first-degree relatives or in at least two generations; early onset breast and ovarian cancer; the presence of associated malignancies in other family members (particularly ovarian cancer but also male breast cancer, pancreatic, prostate, or bilateral breast cancer); multiple primaries in the same individual; and ethnic ancestry associated with a founder mutation (see Table 2). It is important to note that despite the fact that BRCA1/2 mutations are inherited in an autosomal dominant fashion, cancers can skip generations due to the fact that about 15–45% of female carriers never develop cancer, and that male carriers have a low risk of developing cancer. Such a situation may obscure the detection of an autosomal dominant pattern of inheritance; nonetheless, these carriers can still pass on the mutation to their offspring.

Ethnic ancestry has been noted to be predictive for detecting a BRCA1/2 mutation within a family. While so-called “founder” mutations have

Table 2. Characteristics of high-risk BRCA1/2 families

- Early onset breast and/or ovarian cancer
- Multiple primary breast and/or ovarian cancers in the same individual
- Associated cancers (e.g. male breast, pancreatic)
- Autosomal dominant pattern of inheritance
- Ethnic ancestry associated with founder mutations

been observed in specific populations (e.g. Icelandic, Swedish), the strongest founder effects have been noted in Ashkenazi Jews (descended from Eastern or Central Europe) [34]. Two BRCA1 mutations, 185delAG and 5382insC, and one BRCA2 mutation, 6174delT, have been observed with increased frequency in Ashkenazi Jews both with and without a strong family history of cancer. A recent study has shown a high gene frequency for all three of these mutations in a Jewish population unselected for a family history of cancer—about 0.8% for 185delAG, 0.4% for 5382insC and 1.2% for 6174delT [8]. This finding translates to a carrier frequency for these three mutations of about 1 in 45 in Jewish women and men. In comparison, the combined frequency of all BRCA1 mutations in non-Jewish populations is estimated to be between 1 in 500 to 1 in 833 [35]. Because BRCA2 mutations appear to account for a lower proportion of hereditary breast cancer than BRCA1, it is likely that carrier frequency of BRCA2 in the general population is even lower.

Studies in Jewish cancer patients have also demonstrated a high carrier frequency rate for the common mutations—21% of Jewish breast cancer patients unselected for family history diagnosed at age 40 or less [36], and 38% of Jewish ovarian cancer patients diagnosed prior to age 50 carried the 185delAG mutation [37]. Another study carried out in Israel examined the frequency of the three common founder mutations in 199 Ashkenazi Jewish women with breast and/or ovarian cancer [38]. Of these women, 99 had no family history of breast or ovarian cancer. It was observed that 30% of the breast cancer patients under the age of 40 and 62% of the ovarian cancer patients tested positive for one of the three mutations. Of note, 10% of the patients without any family history of cancer had one of these mutations. Thus, for individuals of Jewish descent, simply having one family member with early onset breast or ovarian cancer appears to be associated with a reasonable likelihood of finding a BRCA1 or BRCA2 mutation. In addition, in such families, the likelihood of finding one of the three common mutations increases dramatically when there is a very strong family history of breast and particularly ovarian cancer in a pattern consistent with dominant inheritance. However, it is important to note that novel BRCA mutations have been reported in individuals of Jewish descent and that an increasing number of high-risk Jewish families do not harbor any detectable mutations in BRCA1 or BRCA2 [39]. Earlier studies had predicted that up to 90% of Jewish families with a strong history of breast and ovarian cancer would have one of the three founder mutations [20].

Studies that have systematically assessed the probability of detecting a BRCA1 or BRCA2 mutation have been published [40, 41]. For example, a large multi-institutional study used logistic regression to determine that women with breast cancer before age 50 who also have at least one relative with breast cancer diagnosed less than age 50 or ovarian cancer at any age have at least a 25% chance of carrying a BRCA1 or BRCA2 mutation (the odds increase with the number of affected relatives) [41]. The observed probabilities also showed, as predicted, that Jewish ancestry in high-risk women was associated with a significant likelihood of harboring a BRCA1 or BRCA2 mutation, usually one of the three founder mutations (43% in this series) [41]. Although not formally addressed in the cited studies, the observation of rare cancers such as male breast cancer and pancreatic cancer should alert the clinician to the possibility of detecting a BRCA2 mutation.

Although mathematical models have been developed to assist the clinician in predicting BRCA1/2 carrier probabilities, an important, albeit subtle point that patients must understand is that there is a difference between the chance that the cancers in their family are hereditary and the chance that a detectable mutation will be found in their family, thereby maximizing the likelihood of an informative test result [42]. In fact, the study of 238 high-risk women by Frank et al. [41] revealed that only 39% carried deleterious BRCA1 or BRCA2 mutations, suggesting that other susceptibility genes are likely to account for a proportion of the remaining cases [41]. As testing progresses, further data should emerge to guide clinicians in ascertaining a particular individual's risk of carrying a deleterious mutation in either BRCA1 or BRCA2. Given the expense of testing and the limitations of test result interpretation in low-risk women, probabalistic information is helpful in determining which individuals have the most potential to gain risk information as a result of genetic testing.

Implications of Genetic Testing

It is crucial for patients to understand fully the complexities of genetic testing prior to providing a blood sample for testing. Thus, as part of the informed consent process, a review of the potential benefits, limitations and risks of testing is essential. In addition, unlike most medical procedures, the implications of genetic testing extend not only to the individual being tested, but also to his or her family members.

Benefits of Testing

It is important to note that the benefits of genetic testing for hereditary cancer are as yet unproven. However, potential benefits include:

Increased Knowledge about Cancer Risks

The information gained from genetic testing may help tailor an appropriate cancer screening regimen, as well as allow more informed decision-making about cancer prevention options, including prophylactic surgery and chemoprevention. For individuals who test positive, more intensive screening and consideration of prevention options is recommended. Standard screening guidelines are recommended for those with true negative test results. In addition, some individuals may wish to use genetic testing results to help guide decisions about childbearing and other lifestyle issues.

Information for Family Members

The information obtained from testing may enable close relatives to learn more about their cancer risks. This is particularly true for the relatives of individuals with an alteration in BRCA1 or BRCA2, given that these family members may now be offered the opportunity to be tested. In addition, children of individuals who are found to have true negative test results (i.e. individuals from families with known mutations who are found to test negative for that mutation) can usually be reassured that their cancer risks are now those seen in the general population.

Psychological Relief

The reduction in uncertainty derived from obtaining a test result is a potential benefit of testing.

Insurability

Members of high-risk families who test negative for a known mutation in their family may be less likely to compromise their insurability. Because these individuals would now face the general population risks for cancer instead of the elevated risks noted in mutation carriers, it is possible that insurance companies would be less likely to consider these individuals poor candidates for coverage.

Risks and Limitations of Testing

There are risks and limitations for testing not only for those who test positive but also for those who test negative. These risks and limitations include:

Insurance and Employment Discrimination

The possibility of health insurance discrimination is one of the major issues facing individuals considering testing in the United States. At the present time, fewer than half of the states have laws restricting the extent to which genetic information may be used by health insurers. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer and use the answers in their underwriting decisions. However, recently enacted federal legislation may help to protect those individuals who decide to undergo genetic testing. The Health Insurance Portability and Accountability Act of 1996 recognizes "genetic information" as protected medical information, and forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs.

The Act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution that is greater than that for a similarly situated individual enrolled in that plan. A limitation of the Act is that the premiums charged for individual health insurance are not restricted by the Act, and need only comply with state law. These insurance reform provisions of the Act went into effect on July 1, 1997. Other federal legislation, such as the Genetic Information Nondiscrimination in Health Insurance Act of 1997, is expected to expand on these protections.

Emotional Implications

It has been observed clinically that individuals who test positive often experience some feelings of mild depression, anger, or anxiety. One study documented that mutation carriers with no history of cancer or cancer-related prophylactic surgery had higher levels of psychological distress compared to noncarriers [43]. However, in another study of high-risk kindreds who received genetic counseling in a research setting, individuals who tested positive had no significant increase in either depression or functional impairment within one month of receiving their test result [44]. While non-carriers with true negative results may be relieved about their results and actually show statistically significant

reductions in depressive symptoms [44], some adverse effects are possible such as the manifestation of "survivor guilt." In addition, these individuals may experience a false sense of security about their remaining cancer risk. Therefore, counseling should reinforce the need for them to adhere to the standard cancer screening recommendations.

Impact on Family Dynamics

Unlike most medical procedures, results of genetic testing affect not only the individual being tested, but also his or her relatives. This impacts the approach both to initiating testing within a family and to communicating test results. If a mutation is identified, careful pedigree analysis may reveal that, in addition to siblings and children, a significant number of more distant relatives may be at risk for inheriting the identified mutation. While it is important to convey this knowledge to the patient, it is also important to recognize that communicating such information may place a large burden on the patient, who may not want to contact these relatives or compromise the privacy of information relevant to her test result or cancer history. Family communication patterns are highly variable, and although some individuals may want to share test results openly, others may not. Clinicians must balance the need to respect the patient's wishes regarding this issue while also ensuring that patients are informed about the implications to their family members. Genetic counseling often allows the patient to explore ways in which family communication and overall coping can be facilitated.

Possibility of a False or Inconclusive Result

In addition to a small chance of laboratory error, the possibility of obtaining either a false negative, false positive, or inconclusive test result exists. The interpretation of these findings will be discussed in greater detail in the section on testing outcomes. It is important to note that there are possible psychological ramifications and medical implications that arise in these situations. For instance, individuals from very high-risk families who test negative for mutations in both BRCA1 and BRCA2 may experience some distress due to lingering uncertainty about the etiology of the cancer in their family as well as the cancer risks for themselves and their relatives.

Lack of Proven Methods of Screening and Prevention

The suggested guidelines for medical management for BRCA1 and BRCA2 mutation carriers are outlined below. At present, none of the suggested interventions has been proven to be effective in these individuals. In addition, these procedures may not be covered by insurance carriers.

Logistics of Testing

The cost of commercial testing can be prohibitively high—ranging from about \$300 to \$2400. Not only is it unclear to what extent insurance companies will reimburse this expense, but many individuals are reluctant to seek reimbursement for fear of divulging information about testing to their insurers. The turnaround time for obtaining test results has decreased significantly in the last couple of years, although in some instances, the waiting time may still be considerable. For those patients hoping to use this information to guide medical decision-making, this wait may still prove to be too long.

Process of Genetic Testing

Once a high-risk family is identified, genetic counseling and testing should be offered first to a family member with a diagnosis of early onset breast or ovarian cancer. Such an approach maximizes the likelihood of obtaining an informative test result. For example, if a family member with breast or ovarian cancer diagnosed at a young age tests negative after complete BRCA1 and BRCA2 gene analysis, then it is less likely that a BRCA1/2 mutation explains the cancers observed in the family. If, on the other hand, an unaffected family member undergoes testing first and tests negative, it would not be possible to determine if this result was obtained because there is no BRCA1/2 mutation present in the family or simply because he or she is a non-carrier. Thus, such a finding would not exclude the possibility that a mutation was present in another family member.

The actual testing consists of a blood test. The testing process differs from laboratory to laboratory—some do complete BRCA1 and BRCA2 testing, whereas others test first for the most commonly identified BRCA1/2 mutations. If a disease-conferring mutation is found, then testing may be extended to other at risk relatives. This includes first-degree relatives, and in many cases, more distant relatives such as aunts, uncles, and cousins. The standard approach is to test these family members only

for the presence or absence of the specific mutation identified in their kindred.

In high-risk families of Ashkenazi Jewish descent, if it is not possible to initiate testing in an affected individual, it is reasonable to test an unaffected relative for the three mutations commonly identified in Jewish individuals (185delAG, 5382insC, and 6174delT). A negative test result in this situation, however, does not rule out the possibility of an inherited cancer susceptibility. In addition, in Jewish families in which a BRCA1/2 mutation has been identified, it is recommended that at-risk relatives receive testing for all three common mutations, not just the mutation already found in the family [20].

As part of the process of offering genetic testing, it is essential that genetic counseling be made available to all individuals seeking testing. This should be provided both before testing is undertaken and at the time of the disclosure of the test result.

BRCA1 and BRCA2 Testing Outcomes

There are several possible outcomes from genetic testing. These include a true positive, a true negative and an inconclusive result. A true positive result occurs when a disease-conferring mutation is identified, which is clearly associated with increased risks for breast, ovarian, and possibly other cancers. When a disease-conferring mutation has been identified in the family (usually in a close relative such as a parent or sibling), and is not found to be present in the individual being tested, the result is classified as a true negative, as illustrated in Fig. 1. However, as demonstrated in Fig. 2, the absence of BRCA1 or BRCA2 mutation in the affected proband may be interpreted as an inconclusive finding. This is true whether the patient received only partial testing (e.g. for alterations in only one gene or for common mutations in one or both genes) or complete BRCA1/2 analysis. Possible explanations for this include: 1) the occurrence of a sporadic, non-hereditary cancer; 2) if only partial testing is performed, it is possible that a mutation is present in an untested portion of BRCA1/2; or 3) if complete testing is performed, a mutation could be present in either a regulatory region of the gene or in another gene predisposing to hereditary breast cancer. A second type of inconclusive result occurs when a BRCA1 or BRCA2 alteration is identified, but is of unknown clinical significance. This alteration may be a benign polymorphism or may be a deleterious mutation.

Ashkenazi Jewish

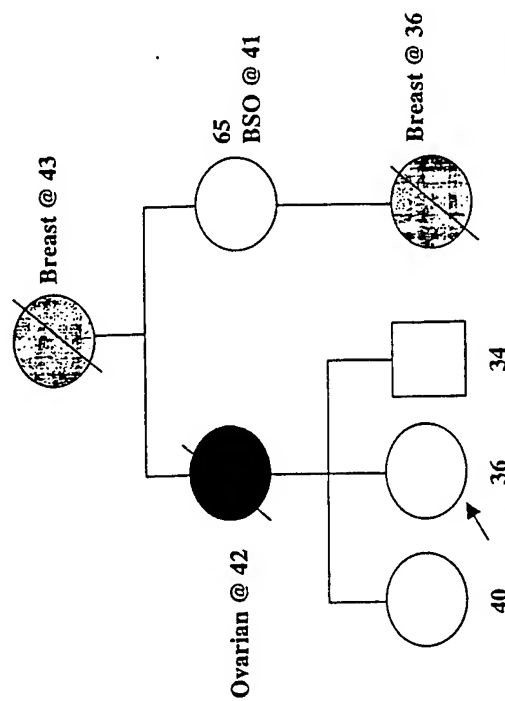


Fig. 1. This pedigree illustrates several different issues. In many families there are no living affected individuals available for testing. Because this family is Jewish, testing for the 3 common mutations was first offered to the proband (♀). She tested negative for these mutations. This result was therefore considered inconclusive. Her older sister was then tested and found to be positive for the 185delAG mutation. Given this finding, the proband's result can now be interpreted as a true negative and she can be reassured about her cancer risk. In addition, their maternal aunt, who is alive without cancer at age 65, is now presumed to be an obligate carrier. The fact that she had a bilateral oophorectomy (BSO) in her 40s may, in part, explain why she is a non-penetrant carrier.

Medical Management for Mutation Carriers

Screening and prevention options

At present, there are no proven methods of cancer screening or prevention in individuals with an inherited susceptibility to cancer. The guidelines outlined below were modified from those set forth by Cancer Genetics Studies Consortium, a group of experts convened by the National Institutes of Health [45].

Irish

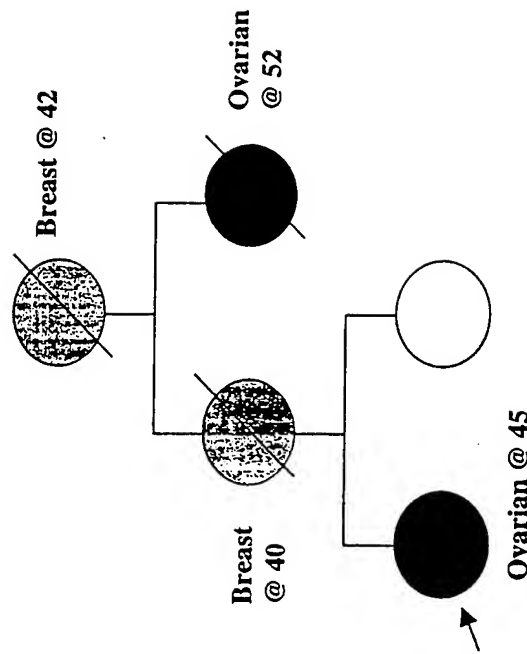


Fig. 2. Complete BRCA1 and BRCA2 testing was performed on the proband (↗) and no mutation was identified. Given the strong family history of early onset breast and ovarian cancer, this finding does not rule out the possibility of an inherited predisposition to breast and ovarian cancer. The potential reasons for this finding are outlined in the text

Breast Cancer

Screening Guidelines

Monthly breast self-examination, clinician exams every 3 to 6 months, and annual mammography. It is recommended that annual mammography begins between the ages of 25 and 35. The efficacy of breast self-exam, clinician exam, and mammography in BRCA1/2 carriers has not yet been demonstrated.

Prevention Options

It is recommended that prophylactic bilateral total mastectomy be discussed with mutation carriers. At present, little data exist to evaluate the efficacy of this surgery. However, it is clear that such an approach does not completely eliminate the risk of developing breast cancer. Two

groups have reported their experience with prophylactic mastectomy. A study from the Mayo Clinic of 950 women who underwent prophylactic bilateral mastectomy used the Gail model to predict the expected numbers of cases of breast cancer. This study included 287 women who had a family history strongly consistent with hereditary breast cancer. With a median follow-up of 17 years, a highly significant 90% reduction in risk of breast cancer was noted in all groups of patients including those with a very strong family history [46]. A second study demonstrated that in a group of 510 high risk women, of which 210 had a positive family history, 1.18% went on to develop invasive breast cancer after either prophylactic total or subcutaneous mastectomy [47]. It is important to note that there are significant limitations in applying the results of these reviews to the anticipated outcome in BRCA1/2 carriers. First, it is now widely agreed that subcutaneous mastectomy is not an acceptable option for prophylaxis, given that a significant amount of residual breast tissue remains. Second, the definition of family history used in these studies was quite broad. Thus, it is likely that many women who chose to undergo this procedure were not members of true hereditary breast cancer families. In addition, given that these studies took place before genetic testing was available, even for those members of high risk families, one would anticipate that at most one half inherited an alteration in a breast cancer susceptibility gene. Studies focusing on known mutation carriers who have undergone prophylactic mastectomy are planned and should provide clearer answers on the efficacy of this approach. Another possible prevention option for high-risk women is participation in chemoprevention trials. Early results from a large randomized trial of tamoxifen, carried out by the NSABP, demonstrated that tamoxifen reduced the risk of breast cancer by 49% in high-risk healthy women [48]. A subset analysis will evaluate the impact of tamoxifen in BRCA1/2 carriers. In addition, other chemoprevention trials will become available in the future.

Ovarian cancer

Screening Guidelines

The current recommendations for ovarian cancer screening include pelvic exam, CA-125 blood tests, and transvaginal ultrasound with color Doppler every 6–12 months beginning at age 25–35. In the general population, these measures have not proven to be very sensitive in detecting early stage ovarian cancer. It is unclear how efficacious these procedures are in a high-risk population.

Prevention Options

It is recommended that prophylactic oophorectomy be considered in women with a BRCA1 alteration or BRCA2. An NIH consensus conference convened in 1994 recommended prophylactic oophorectomy at age 35 or when childbearing is complete for women from hereditary ovarian cancer families [49]. A more recent review by the Cancer Genetics Studies Consortium recommended that such an approach be considered, but did not endorse it given the lack of evidence regarding its efficacy [45]. Observational studies have documented a residual risk of primary peritoneal carcinomatosis in members of high-risk families who have undergone prophylactic oophorectomy. A report from the Gilda Radner Familial Cancer Registry demonstrated a 2% (6 cases among 324 women) failure rate [50]. An NIH study of 12 breast/ovarian families showed 2 cases of peritoneal carcinomatosis in 460 person-years in a group of oophorectomized women as compared with 8 cases of ovarian cancer in 1665 person-years in family members who had not undergone oophorectomy. This translated to a 24-fold excess risk of ovarian cancer in non-oophorectomized family members, versus a 13-fold excess of "ovarian" cancer in those who underwent oophorectomy [51]. This difference, however, was not statistically significant. Thus, the extent to which prophylactic surgery reduces the risk of ovarian cancer is unclear. Further research, including a large international study, is planned to address this issue.

Other possible prevention options include the use of chemoprevention agents. It has been demonstrated that women in the general population who have taken the oral contraceptive pill for at least five years reduce their risk of ovarian cancer by about 40% [52, 53]. In addition, a recent study suggested that the oral contraceptive pill reduces the risk of ovarian cancer in BRCA1/2 carriers [26].

Colon Cancer

Screening Guidelines

Fecal occult blood testing coupled with flexible sigmoidoscopy or colonoscopy is recommended beginning at age 50. The endoscopic exams should be repeated every 3-5 years if normal, and the fecal occult blood testing should be performed annually. These recommendations are no different from the screening guidelines for the general population; however, they may be modified in the setting of a family history of colon cancer.

Prostate cancer

Screening Guidelines

Rectal exam and PSA annually beginning at age 50 is recommended. This guideline is no different from the screening recommendation for the general population.

Hormone Use

Oral Contraceptives (OCPs)

The long term use of oral contraceptives in younger women appears to be associated with an increased risk of developing breast cancer before age 40 [54, 55]. Overall, however, OCPs are not associated with a significantly elevated risk of breast cancer [55]. It is unclear if the risk of breast cancer is further increased in OCP users who have a close relative with breast cancer [54, 56]. As discussed previously, a recent study has suggested that among young breast cancer patients, long-term use of OCPs increases the risk of breast cancer significantly more in mutation carriers than in non-carriers [25]. However, studies have demonstrated consistently a protective effect of OCPs on ovarian cancer risk in the general population, which appears to increase with duration of use of OCPs [52, 53]. These findings seem to apply also to mutation carriers [26]. Thus, in the setting of limited knowledge, one must balance the potential benefits of the pill in terms of reduction in risk of ovarian cancer against the possible increase in breast cancer risk in BRCA1/2 carriers. Studies are underway to determine whether risks for breast or ovarian cancer in BRCA1 and BRCA2 carriers are modified by other known reproductive history risk factors.

Hormone Replacement Therapy

Studies have demonstrated that, in women in the general population, long-term use of hormone replacement therapy (HRT) with estrogen alone or estrogen and progesterone, increases the risk of breast cancer (relative risk of 1.2-1.5) [57, 58]. Again, it is important to note that little information exists on the effect of HRT in women who are BRCA1/2 carriers. These women are often considering having prophylactic oophorectomy at an early age and therefore the question about HRT for protection against heart and bone disease as well as relief from menopausal symptoms frequently arises. Some clinicians do not believe that HRT is

necessarily contraindicated for BRCA1/2 carriers who have prophylactic mastectomy and oophorectomy performed at a young age. However, at present there is little information available to guide patients and their physicians who are considering this option.

Individualizing a Screening/Prevention Program

It is important for individuals undergoing genetic testing to understand that there are no proven means of cancer prevention or screening in mutation carriers. Thus, each carrier should be encouraged to take the time to fully weigh the implications of different management approaches prior to deciding on a particular plan. It is also not infrequent for an individual's approach to change over time. For example, a young woman may choose surveillance for ovarian cancer if she has not yet completed childbearing. Once her family is complete, she may then wish to consider prophylactic surgery.

Conclusion

While it took many years to clone BRCA1 and BRCA2 after the initial identification of high-risk families, much information has been elucidated about these genes in the short time since then. The molecular structure of BRCA1/2 has been characterized and research is underway to learn more about the BRCA1/2 protein products, how they function as tumor suppressors, and how these proteins may interact with biologic and environmental modifiers of gene expression. It is also likely that more precise genotype-phenotype correlations will emerge. With the identification of hundreds of mutations in these genes, new technologies are being developed to improve the sensitivity and specificity of testing. All of this information will be critical in providing more accurate risk assessments, particularly for those individuals with less striking family histories.

Increasing knowledge about the clinical manifestations of BRCA1/2 alterations will help practitioners determine who is an appropriate candidate for testing based in part on the likelihood of finding a mutation in the family. Patients, particularly those with a strong family history of cancer, appear to accept the ambiguity in what is known with respect to cancer risks. However, long-term data regarding the effectiveness of the available screening and preventive strategies for mutation carriers are eagerly awaited. In addition, it will be important to initiate or continue prospective studies regarding the impact of potential risk modifiers in mutation

carriers (e.g. hormone replacement therapy, oral contraceptives, tamoxifen, etc.).

In the meantime, individuals considering genetic testing must do so in the context of the uncertainties that exist in the present time. Aside from limited knowledge about cancer risks and management options, the psychological effects of risk notification are relatively unknown, especially in the long term. Because of the magnitude of information that patients must assimilate and the potential psychological sequelae of testing, it is critical that patients have access to genetic counseling before and after testing. This process enables patients to provide properly obtained informed consent, and to make their own choices about getting tested and about management options based on currently available information. To guide the clinician, several organizations, including the American Society of Clinical Oncology and the National Society of Genetic Counselors, have published position statements regarding the indications for testing and the components of genetic counseling [59, 60]. The general principles set forth in those statements, as well as in this and other documents, will no doubt be considered as we prepare for the inevitable isolation of additional breast and ovarian cancer susceptibility genes and the subsequent patient interest in testing.

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Acknowledgments: We gratefully acknowledge Lenora Johnson, MPH, CHES and Aba Bonney, BS for their invaluable assistance with manuscript preparation. We would also like to thank Caryn Lerman, PhD and Barbara Brogan, RN, MS for their thoughtful review of the manuscript.

Clinical Applications of Angiogenesis Inhibitors

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Introduction

Most deaths from cancer result from the relentless growth of metastases that are resistant to conventional therapies [1]. Significant improvements in therapy of metastasis depend on a better understanding of the biology of the metastatic process which can provide a sound basis for the design of specific antimetastatic regimens. This chapter reviews recent data on the role of angiogenesis in metastasis and how its regulation may inhibit disseminated cancer.

The pathogenesis of cancer metastasis consists of a series of linked, sequential, and selective steps. Metastasis begins with the detachment of tumor cells from the primary neoplasm and the invasion of the surrounding stroma by single cells or a group of cells with increased motility and secretion of degradative enzymes. Once the invading cells penetrate the lymphatic or vascular channels, they may grow there or a single cell or clumps of cells may detach and be transported within the circulatory system. Tumor emboli must survive the host's immune and nonimmune defenses and the turbulence of the circulation, arrest in the capillary bed of receptive organs, extravasate into the organ parenchyma, proliferate, and establish a micrometastasis. Growth of these small tumor lesions requires the development of a vascular supply and continuous evasion of host defense cells. When the metastases grow, they can shed tumor cells into the circulation and thus produce metastasis of metastases [1].

In 1889, Paget proposed that metastasis was not random and occurred only when certain favored tumor cells (the "seed") interacted with certain specific organs (the "soil") [2]. A modern definition of the "seed and soil" hypothesis consists of three principles. First, neoplasms are biologically heterogeneous and contain subpopulations of cells with different metastatic properties [1]. Second, the process of metastasis is selective for cells that preexist in the parental neoplasm [3]. Third, the outcome of metastasis, as shown in human and rodent tumors, depends on multiple interactions of metastatic cells with homeostatic mechanisms shown to influence growth, vascularization, invasion, and drug sensitivity [4].

Evaluation and Management of Women with a Strong Family History of Breast Cancer

Claudine J. D. Isaacs, Beth N. Peshkin, and Caryn Lerman

As breast cancer risk factors, including the impact of a positive family history, become better understood, genetic counseling and testing are being increasingly integrated into the management of women at high risk for this disease. When family histories suggest transmission of genetic risk, high-risk women and their family members may benefit from participation in counseling and testing programs. High-risk women potentially can reduce their risk of cancer morbidity and mortality through increased surveillance and adoption of risk-reducing strategies. Noncarriers of risk-conferring mutations may be relieved of persistent worry. Despite these possible benefits, testing carries a number of psychological and social risks that patients and providers must consider. These include adverse psychological effects in individuals and families and the chance of insurance discrimination.

Although genetic counseling and testing for breast cancer are diffusing into mainstream oncologic care, critical questions regarding cancer risks, the benefits of genetic testing, and the efficacy of management options remain unanswered. These limitations in knowledge create challenges for the providers who must counsel patients about these issues and for the patients who face these decisions. This chapter provides an overview of the medical and psychosocial issues relevant to this process. The chapter focuses on high-risk patients who have family histories consistent with inherited susceptibility to breast cancer and who have been deemed appropriate candidates for genetic testing by major medical organizations.¹ The evaluation and management of women with less suggestive family histories are also addressed. The assessment of the likelihood that a family harbors a breast cancer-predisposing mutation is first examined, followed by a discussion of cancer risks in mutation carriers. The genetic counseling process and laboratory testing issues are then reviewed. Finally, the

medical and psychosocial management issues for high-risk individuals and families are discussed.

ASSESSMENT OF THE PROBABILITY OF INHERITED SUSCEPTIBILITY

Of the many factors known to influence a woman's risk of breast cancer, family history and increasing age are among the most significant. Estimates are that 20% to 30% of women with breast cancer have at least one relative with this disease,^{2,3} and 5% to 10% have a true hereditary predisposition to breast cancer.⁴ Thus, the majority of women with a family history of the disease do not have hereditary breast cancer but rather have a familial basis to their disease. Most hereditary breast cancers arise from mutations in *BRCA1* and *BRCA2*. Registry-identified families with deleterious mutations in these genes often have cancer histories extending over many generations and thus provide unmistakable clues about the hallmarks of hereditary breast cancer. As illustrated in Fig. 1, these features include the presence of multiple relatives affected with breast or ovarian cancer, usually with a predominance of early-onset cases; the presence of women with more than one primary cancer, such as bilateral breast cancer or breast and ovarian cancer; and vertical transmission, including transmission in two or more generations as well as through male relatives (consistent with autosomal dominant inheritance). In addition, the occurrence of rare malignancies or certain hallmark features may be suggestive of a specific syndrome or gene mutation. For example, early-onset sarcomas and breast cancers are suggestive of Li-Fraumeni syndrome, whereas the presence of hamartomas is suggestive of Cowden disease.

When performing risk assessments for hereditary breast cancer, in addition to obtaining family medical history, the clinician should also inquire about the patient's ethnic background, as specific mutations in *BRCA1* and *BRCA2* have been found to occur with increased frequency in certain populations. For example, two *BRCA1* mutations, 185delAG and 5382insC, and one *BRCA2* mutation, 6174delT, have been found with increased frequency in individuals of

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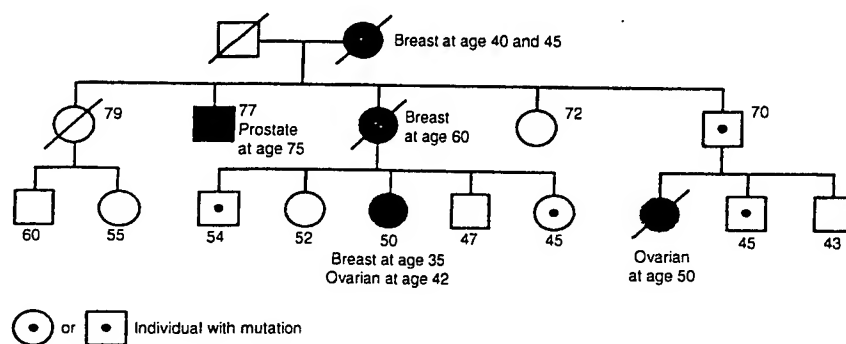


FIG. 1. This pedigree illustrates classic features of hereditary breast cancer. An autosomal dominant pattern of inheritance is clearly demonstrated; three generations are affected, and approximately 50% of offspring at risk carry the mutation. Other characteristic features of hereditary breast cancer include early onset of breast and ovarian cancer, bilateral breast cancer, and multiple primary cancers in the same individual. Note that transmission through men is also possible.

Ashkenazi Jewish descent.⁵ The impact of founder mutations on the likelihood of detecting a mutation in *BRCA1* or *BRCA2* is discussed in greater detail below.

In practice, the ability to discern a pattern of hereditary breast cancer may be hampered by a variety of factors. These include the genes' variable expressivity and incomplete penetrance. In addition, many individuals have limited knowledge about their family histories. Kindreds may also be small in size or may not be highly informative. For example, families may contain many men relative to women at risk, women who died young, or individuals not yet old enough to exhibit the phenotype.

Given all of these considerations, when a patient's family history is deemed to be suggestive of hereditary breast cancer, risk assessment is based on probabilistic estimates of finding a gene mutation, the chance that the individual is a gene carrier based on Mendelian analysis, and the risk of cancer based on estimates of gene penetrance. In cases in which a patient's history is not highly suggestive of hereditary breast cancer, however, empiric models are available to estimate risk of breast cancer.

Empiric Models of Risk Assessment

The Cancer and Steroid Hormone (CASH) Study, a population-based, case-control study, fit genetic models to derive age-specific breast cancer risk estimates for women with at least one relative with breast cancer.⁶ Risk tables from this model are available that allow the clinician to assess risk based on the relatives' age at diagnosis and the degree of relationship of these relatives. For example, a woman with one first-degree relative with breast cancer diagnosed in her thirties is estimated to have a 16% lifetime risk of developing breast cancer. This model also predicted breast cancer risk of women with a very strong family history of the disease. Thus, a woman with two first-degree relatives with breast cancer, one diagnosed at age 45 and the other at age 52, is predicted to have a lifetime risk of breast cancer of approximately 30%. However, if both these relatives were diagnosed in their twenties, the woman's risk is estimated to be approximately 48%. One must remember that this model predated the identification of *BRCA1* and *BRCA2* and is based on the

possibility that a rare autosomal dominant allele is segregating in the family. Now that *BRCA1* and *BRCA2* have been cloned, the probabilistic models described below may also be useful for assessing the likelihood that an individual with a strong family history of breast cancer harbors a mutation in one of these genes. This information, in turn, can be used to estimate her risk of cancer.

Another model, known as the Gail model, is based on data from the Breast Cancer Detection Demonstration Project. This model uses the following risk factor information to derive age-specific breast cancer risk estimates: age at menarche, age at first live birth, number of previous biopsies, presence of atypical hyperplasia or lobular carcinoma *in situ*, and number of first-degree relatives with breast cancer.⁷ Data for an individual patient can be analyzed using a computer program developed by the National Cancer Institute or extrapolated from graphs.⁸ For example, a 45-year-old woman with menarche at age 11, a first full-term pregnancy at age 26, one first-degree relative with breast cancer, and no prior breast biopsies is estimated to have a 1.8% 5-year risk and a 19% lifetime risk (to age 90) of breast cancer. If this woman had two first-degree relatives with breast cancer rather than just one, her 5-year risk of breast cancer would increase to 3.1% and her lifetime risk to 32%. If, on the other hand, this woman had no relatives with breast cancer, her 5-year risk of cancer is estimated at 1%, and her lifetime risk is estimated at 12%. Limitations of this model are the inclusion of a nonbiological variable (i.e., the number of breast biopsies may be influenced by patient or physician concern due to family history) and the exclusion of more extensive family history information, including information from all paternal relatives and the ages at diagnosis of cancer. Whereas the inclusion of any biopsy history may falsely elevate risk, omission of family history data may lead to a sizable underestimation of risk. Validation studies of this model revealed that, in certain circumstances, it overestimated cancer risk. Data from the Nurses' Health Study found that the Gail model overpredicted the absolute risk of breast cancer by 33% for women between 25 and 61 years of age who did not undergo annual mammography screening.⁹ A second study found that the Gail model provided a good estimation of cancer risk for women who participated in regular cancer screening; however, it overpredicted the

risk for women not adhering to screening recommendations as well as for those under the age of 60, and underpredicted the risk for those over age 60.¹⁰

Risk estimates for the same woman based on CASH and Gail models have been compared and were found to be discordant in several circumstances, in part because of the different parameters of the models.¹¹ Thus, no model is appropriate for every patient. However, the information may be interpreted qualitatively to get a sense of whether the patient is at a somewhat higher risk of developing breast cancer or at a very high risk for the disease. Screening and prevention programs may then be tailored to the risk level of the patient.

Probabilistic Estimates and Models of Risk Assessment for Individuals with Family Histories Suggestive of Hereditary Breast Cancer

Founder Mutations

An important aspect of accurate assessment of hereditary risk is documentation of the pedigree and the patient's ethnic background. For example, the carrier frequency for *BRCA1* mutations in the general population is between 1 in 500 and 1 in 800¹² and is lower for *BRCA2*; however, in individuals of Ashkenazi Jewish descent, two *BRCA1* mutations (185delAG and 5382insC) and one *BRCA2* mutation (6174delT) occur with a background frequency of 2.3%.¹³ In light of this high background frequency, it is not surprising that 50% to 90% of Jewish families with strong histories of breast and ovarian cancer harbor one of these founder mutations.^{5,14} In addition, studies have been performed in breast and ovarian cancer patients of Ashkenazi Jewish descent who were unselected for family history. Those with breast cancer diagnosed at age 40 or younger were found to have a 21% chance of carrying the 185delAG mutation,¹⁵ and 38% of ovarian cancer patients diagnosed before age 50 carried the 185delAG mutation.¹⁶ Another study conducted in Israel examined the frequency of the three common founder mutations in 199 Ashkenazi Jewish women with breast or ovarian cancer (or both).¹⁷ Of these women, 99 had no family history of breast or ovarian cancer. Thirty percent of the breast cancer patients younger than age 40 and 62% of the ovarian cancer patients tested positive for one of the three mutations. Thus, for Jewish individuals, one case alone of early-onset breast or ovarian cancer is sufficient history to warrant consideration of *BRCA1* and *BRCA2* testing.

As reviewed by Szabo and King, founder mutations have been identified in other ethnic subpopulations, including those in Iceland, Finland, France, Holland/Belgium, Russia, Sweden, and Denmark.¹⁸ The attributable risk of *BRCA* mutations in these populations varied considerably. For example, in Russia, 79% of families with breast and ovarian cancer had one of two common *BRCA1* mutations; one of these, 5382insC, occurs quite frequently in Europeans in

general, including Ashkenazi Jews. The other mutation, 4153delA, appears to occur only in Russians. Similarly, in Israel, the three Jewish founder mutations accounted for a high proportion (47%) of hereditary breast and ovarian cancer, as would be expected. However, in Italy, only 29% of high-risk families had a *BRCA1* mutation, and almost all of them were unique mutations. As additional studies are undertaken, a pattern of recurrent mutations may emerge in additional populations, as suggested by some preliminary data from African-American families.¹⁹ In addition, a study showed that six *BRCA1* and *BRCA2* mutations were found in 40% of high-risk French Canadian families.²⁰ Overall, *BRCA2* mutations occur less frequently than *BRCA1* mutations. However, in Iceland, a single *BRCA2* mutation, 999del5, accounted for a substantial proportion of breast and ovarian cancer cases in that country.^{21,22} Thus, information about the genetic epidemiology of *BRCA1* and *BRCA2* in different populations may assist the clinician in determining the likelihood of a hereditary susceptibility to breast cancer as well as the type, extent, or sequence of testing to be performed in particular subsets of patients.

Probabilistic Models

In addition to assessments related to ethnic ancestry, probabilistic models have been developed to assist the clinician in determining the likelihood that an individual harbors a *BRCA1* or *BRCA2* mutation. One study used a logistic regression analysis to predict the probability of detecting a *BRCA1* mutation given various factors in a woman's medical and family history.²³ Twenty institutions in North America and Europe pooled *BRCA1* data on 798 high-risk women from distinct families. In 102 women, a deleterious mutation was identified. The age of the proband, personal cancer history, Ashkenazi Jewish ancestry, and family history were all found to significantly influence the likelihood that these mutations would be detected. The odds of detecting a *BRCA1* mutation decreased by 8% with each year added to the proband's age at diagnosis. The odds were increased by personal cancer history, strong family history, and Ashkenazi Jewish ancestry. When women with unilateral breast cancer were used as the comparison group, the odds were found to increase 3.7-fold for those with bilateral breast cancer, 5.4-fold for those with ovarian cancer, and 8-fold for those with unilateral breast cancer and ovarian cancer. Odds also increased 2.9-fold for each relative with ovarian cancer, 5.3-fold for each relative with both breast and ovarian cancer, and 1.4-fold for each relative with breast cancer alone. In addition, an Ashkenazi Jewish woman's chance of carrying a deleterious mutation was 4.1 times that of a non-Ashkenazi woman. For example, in Jewish families with at least two cases of breast cancer and one case of ovarian cancer, the chance of finding a *BRCA1* mutation is 75%. In non-Ashkenazi families with the same history, the probability drops to 33%. A smaller study of 169 women referred to a

TABLE 1. Modeled probabilities of detecting a *BRCA1* or *BRCA2* mutation

Family history parameter	Likelihood of <i>BRCA1</i> mutation	Likelihood of <i>BRCA2</i> mutation
Single affected individuals (no other family history)		
Breast cancer at <30 yr	12%	n/a
Breast cancer at <40 yr	6%	n/a
Jewish woman with breast cancer at <40 yr	33%	n/a
Two or more cases of breast/ovarian cancer in FDR or SDR		
≥2 breast cancers at ≥50 yr	2%	n/a
1 breast cancer at 40–50 yr and 1 breast cancer at <50 yr	10%	14.5%
1 breast cancer at 40–50 yr and FDR or SDR with ovarian cancer	23%	12.5%
1 breast cancer case at 40–50 yr with bilateral breast cancer or ovarian cancer and FDR or SDR with breast cancer at <50 yr	42%	10%
1 breast case cancer at 40–50 yr with bilateral breast cancer or ovarian cancer and FDR or SDR with ovarian cancer	65%	6%

FDR, first-degree relative; n/a, not available; SDR, second-degree relative.
Adapted from refs. 23 and 25.

high-risk clinic also found that breast cancer diagnosis at an early age, the presence of ovarian cancer, the occurrence of breast and ovarian cancer in the same individual, and Ashkenazi Jewish ancestry were all associated with an increased risk of detecting a *BRCA1* mutation.²⁴

Newer models have been developed since the cloning of *BRCA2*. The most extensive model is based on a study of 238 women with breast cancer diagnosed before age 50 or ovarian cancer diagnosed at any age and a positive family history.²⁵ This model demonstrated that the presence of ovarian cancer within families significantly increases the chance of finding a *BRCA1* or *BRCA2* mutation. For example, the model predicts that if two women with breast cancer diagnosed before age 50 are first- or second-degree relatives of one another, the probability of finding a *BRCA1* mutation is approximately 10%, and the chance of finding a *BRCA2* mutation is approximately 15%; thus, the combined probability of finding a mutation in one or the other gene is 25%. However, if one of these relatives also had ovarian cancer, the chance of finding a mutation doubles to approximately 50% (a 42% chance of finding a *BRCA1* mutation and a 10% chance of finding a *BRCA2* mutation). An early age of onset for breast cancer (younger than 40 years) and a diagnosis of ovarian cancer in the same woman, in combination with a family history of breast and ovarian cancer, increases the likelihood of finding a *BRCA1* or *BRCA2* mutation to almost 90%. Additional examples are highlighted in Table 1. Although the issue was not addressed quantitatively in the aforementioned study, in a family presenting with rare cancers, such as those of the pancreas or male breast, the clinician may suspect the likelihood of finding a *BRCA2* mutation to be higher.^{26,27} In general, however, *BRCA2* mutations account for a lower proportion of hereditary breast cancer cases than *BRCA1* mutations.

Despite the fact that other studies have found Ashkenazi ancestry to be associated with a significantly increased chance of finding a *BRCA1* or *BRCA2* mutation, the model by Frank et al. did not confirm this finding.²⁵ The authors hypothesized that this may be due to the fact that only fami-

lies with strong histories of breast and ovarian cancer were included; thus, probability estimates may not be significantly impacted by ethnicity in the setting of a strong family history.

A substantial proportion of individuals with a very strong family history of breast and ovarian cancer are not found to have mutations in either *BRCA1* or *BRCA2*.^{24,25} The most probable explanation for this finding is that other as yet undefined genes account for the cancers seen in these families. In addition, methods of testing are unable to detect all disease-conferring mutations in *BRCA1* and *BRCA2*.

In summary, the models outlined provide patients with an estimate of their risk status and the likelihood that *BRCA1* and *BRCA2* gene testing will be informative. In accordance with guidelines set forth by the American Society of Clinical Oncology, individuals with family histories consistent with at least a 10% chance of finding a mutation in a breast cancer susceptibility gene¹ are considered at high risk for breast cancer on the basis of family history and are appropriate candidates for genetic testing. Individuals who have at least one first-degree relative with breast cancer but who do not have a family history strong enough to be consistent with at least a 10% chance of harboring a mutation in *BRCA1* or *BRCA2* or those with at least a 1.66% 5-year risk of breast cancer as determined by the Gail model are considered at moderate risk of breast cancer. Importantly, factors related to family history are only one aspect to be considered by patients in deciding whether to undergo genetic testing. As outlined in the section on Genetic Counseling Process, individuals with a strong family history of breast or ovarian cancer must seriously weigh the benefits, limitations, and risks of testing before deciding whether to pursue testing.

CLINICAL CHARACTERISTICS OF HEREDITARY BREAST CANCER

The majority of cases of hereditary breast cancer is due to mutations in *BRCA1* and *BRCA2*. Rare syndromes that

ovarian cancer after a diagnosis of breast cancer has been estimated to be ten times greater than that of women with sporadic breast cancer.²⁵

Results from a population-based study indicated that men with *BRCA1* and *BRCA2* mutations have a 16% risk of prostate cancer by age 70.¹³ Noncarriers were found to have a risk of 4%. Typically, the age of onset of prostate cancer is the same in *BRCA1* and *BRCA2* carriers as in the general population. In addition, men with a *BRCA2* mutation have been estimated to have up to a 6% chance of developing breast cancer.²⁷ Some studies have also suggested that colon cancer is associated with *BRCA1* mutations³⁰ and pancreatic cancer with *BRCA2* mutations.^{5,26}

In summary, the precise cancer risks for any one mutation carrier are difficult to define. These risks should be interpreted within the context of the individual's own family history. In addition, specific *BRCA1* or *BRCA2* mutations may be associated with different cancer risks.

Cancer Risk Modifiers

Individuals within the same family carrying the same mutation may show significant differences in the age of onset and type of cancer developed. For instance, one woman may develop breast cancer in her thirties; her sister may develop both early-onset breast cancer and ovarian cancer; and a third mutation-positive relative may be healthy in her seventies. This variable penetrance and expressivity of *BRCA1* and *BRCA2* has led investigators to examine the role of environmental risk factors and other genes in modifying the cancer risks of carriers.

A study of the reproductive history of 333 women with *BRCA1* mutations was conducted to shed some light on possible environmental risk modifiers.³⁴ The risk of breast cancer was found to be increased in those who experienced menarche before age 12 (relative risk, 1.57) and in those with parity of less than three (relative risk, 2). Age at first full-term pregnancy was not found to influence the risk of breast cancer. In distinction to what is seen in the general population, the risk of ovarian cancer was found to be higher in those with increased parity, with each additional birth resulting in an increased relative risk of 1.4. However, a protective effect was found for a later age at last birth. Women whose last birth was at age 30 or older had a 48% reduction in risk of ovarian cancer compared with those who were 29 years or younger at last birth.

A case-control study examined the effects of oral contraceptive use on the risk of ovarian cancer in mutation carriers.³⁵ Known mutation carriers with a history of ovarian cancer were compared with their sister controls. The results suggested that oral contraceptive use may reduce the risk of ovarian cancer by as much as one-half in *BRCA1* and *BRCA2* carriers. However, the sister-control group included mutation carriers, noncarriers, and individuals whose mutation status was unknown. In addition, 42% of the control

group had undergone prophylactic oophorectomy. The heterogeneity of the control group and the presence of confounding factors, such as prophylactic surgery, make it difficult to ascertain the true impact of oral contraceptive use in mutation carriers. Nonetheless, this study does suggest that oral contraceptive use offers protection against ovarian cancer in this patient population. A study of 50 young Ashkenazi Jewish breast cancer patients, however, indicated that long-term oral contraceptive use (more than 48 months), particularly before a first full-term pregnancy, was associated with a higher chance of being classified as a *BRCA1* or *BRCA2* carrier; this finding suggests that oral contraceptive use may increase breast cancer risk more in *BRCA1* and *BRCA2* mutation carriers than in noncarriers.³⁶ Thus, in mutation carriers, oral contraceptives may possibly provide protection against ovarian cancer but may also increase the risk of breast cancer. Further studies are needed to address this issue.

Modifier genes may also affect gene penetrance. For example, one group found that the risk of ovarian cancer in *BRCA1* carriers with one or two rare *HRAS1* alleles was approximately two times greater than in carriers with only common *HRAS1* alleles.³⁷ Another study examined allelic variants of *CYP1A1*, a gene involved in the metabolism of polycyclic aromatic hydrocarbons and in the hydroxylation of estradiol, in *BRCA1* and *BRCA2* mutation carriers with and without breast cancer.³⁸ In this study, a particular allelic variant was found in 14% of carriers with cancer and in 22% of unaffected carriers and reduced the risk of breast cancer by approximately 40%. Studies addressing the role of other gene-gene interactions are under way.

Ideally, to best address the impact of gene-gene or gene-environment interactions on the risk of cancer in mutation carriers, studies should be performed only in individuals with a defined *BRCA1* or *BRCA2* mutation. Study designs of this type would allow a clearer evaluation of the effect of a possible risk modifier on cancer incidence in mutation carriers. To date, identification of enough affected and unaffected carriers to carry out studies in this fashion has not been possible. Therefore, further studies are needed to validate the observations from the studies discussed in this chapter. If these findings are substantiated, it may be possible to more specifically determine an individual carrier's cancer risks and to devise tailored risk-reduction strategies.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is an autosomal dominant condition characterized by soft-tissue sarcomas, osteosarcomas, leukemias, brain tumors, adrenocortical malignancies, and early-onset breast cancer. Estimates are that 50% of carriers develop some form of cancer by age 30 years and 90% by age 70 years.³⁹ In particular, the occurrence of breast cancer in these families is remarkable. In a study of 24 Li-Fraumeni syndrome families including 200 individuals, 45 women were

TABLE 2. Estimated cancer risks associated with *BRCA1* and *BRCA2* mutations

Type of cancer	Estimated lifetime risk in <i>BRCA1</i> mutation carriers ^{13,28-30,33}	Estimated lifetime risk in <i>BRCA2</i> mutation carriers ^{5,25-27,31,32}	Lifetime risk in general population
Breast cancer	55%–85%	37%–85%	12.5%
Contralateral breast cancer	Up to 65%	Possibly similar to <i>BRCA1</i> risks	0.5%–1.0% per year
Ovarian cancer	15%–60%	15%–27%	1.4%
Ovarian cancer after breast cancer	Up to 30%–55%	Significantly elevated	2%–3% (approximately twice the average risk)
Prostate cancer	Possible relative risk of 4	Possible increased risk	Approximately 6%
Colon cancer	Increased risk, possibly up to a relative risk of 3	Probable increased risk	At least 10%, but risk is difficult to quantify partially owing to the presence of clinically undetectable cancers
Pancreatic cancer	A few reported cases	Approximately 6%	Extremely rare
	Not increased	Associations noted	Rare

These risks are cumulative and are not mutation specific. In general, early ages of onset have been associated primarily with male breast cancer and ovarian cancer. However, some cases of early-onset pancreatic cancer associated with *BRCA2* alterations have been reported. Relative risks, such as those associated with prostate and colon cancer in *BRCA1* carriers, are not directly translatable to absolute risks. Figures for general population risks include some patients with hereditary cancer. All risks must be evaluated in the context of the patient's medical and family history. Modified from ref. 61.

account for substantially less than 1% of all cases of breast cancer include the Li-Fraumeni syndrome, Cowden disease, Peutz-Jeghers syndrome, Muir-Torre syndrome, and possibly telangiectasia heterozygosity. The cancer risks of individuals with hereditary breast cancer are summarized below.

BRCA1 and *BRCA2*

Cancer Risks

BRCA1 and *BRCA2* carriers have been found to have a wide range of cancer risks (Table 2). The initial studies assessing cancer risks were performed in very highly selected families with multiple cases of breast and ovarian cancer. In these studies, the risk of breast cancer in *BRCA1* and *BRCA2* carriers was estimated to be up to 85%.^{27,28-31} *BRCA1* and *BRCA2* carriers have been found to have an early age of onset of breast cancer in comparison with the general population. Approximately 20% of *BRCA1* carriers develop breast cancer before the age of 40; one-half of carriers develop it by the age of 50.²⁸ *BRCA2* carriers may have a slightly older age of onset of breast cancer than do *BRCA1* carriers. A study found that 32% of *BRCA2* carriers had developed breast cancer by age 50 and 53% by age 60.³¹ In these individuals, the average age of onset of breast cancer was found to be 41 years.²⁶ The risk of ovarian cancer by age 50 was estimated at close to 60% for *BRCA1* carriers^{28,29} and up to 27% for *BRCA2* carriers.²⁹ Subsequently, population-based studies were performed and demonstrated lower cancer risks. The family history information obtained from

population-based studies is often incomplete. Thus, these studies may underestimate cancer risks. A study of 5,000 individuals of Ashkenazi Jewish descent not selected for a family history of breast or ovarian cancer estimated that the risk of breast cancer was 56% by age 70 for carriers of two *BRCA1* mutations, 185delAG and 5382insC, and one *BRCA2* mutation, 6174delT.¹³ The risk of ovarian cancer in this population was found to be 15%. Another population-based study performed in Iceland, which obtained family history only on first-degree relatives, found that carriers of the 999del5 *BRCA2* mutation had a 37% risk of breast cancer by age 70.³² Therefore, for *BRCA1* carriers, the breast cancer risk varies between 55% and 85%, and for *BRCA2* carriers, the risk may be as low as 37% or as high as 85%. The risk of ovarian cancer is estimated to be 15% to 60% for *BRCA1* carriers and between 15% and 27% for *BRCA2* carriers.

Mutation carriers also face an increased risk of second malignancy. *BRCA1* carriers who are affected with breast cancer have been estimated to have a 38% 10-year risk and up to a 65% cumulative risk of contralateral breast cancer.^{28,33} In comparison, individuals with sporadic breast cancer have a 0.5% to 1.0% annual risk of contralateral breast cancer. No conclusive information exists on the risk of ipsilateral recurrence in mutation carriers with breast cancer after breast-conserving surgery and radiation therapy. This subject is discussed in greater detail in Chapter 33. In addition to the increased risk of a second primary breast cancer, the risk for ovarian cancer in *BRCA1* carriers affected with breast cancer has been estimated to be as high as 44% by age 70.²⁸ This compares to a risk of approximately 3% in patients with sporadic breast cancer. *BRCA2* carriers' risk of

found to have developed breast cancer, of whom 73% were diagnosed before age 45.⁴⁰ Multiple breast cancers were diagnosed in approximately 25% of these women, and more than 25% had had other additional primary tumors. Mutations in the tumor-suppressor gene *p53* have been documented in up to 70% of families with Li-Fraumeni syndrome; however, estimates vary depending on the ascertainment criteria used and the extent of gene testing performed.⁴¹ When a mutation is identified, predictive testing may be available to family members at risk. Screening for most of the component cancers of this syndrome is not available, but informing women at risk for Li-Fraumeni syndrome about options for early detection and prevention of breast cancer is critical.

Ataxia-Telangiectasia

Ataxia-telangiectasia is an autosomal recessive condition characterized by immunodeficiency, cerebellar degeneration, oculocutaneous telangiectasias, and a markedly elevated risk of solid tumors and hematologic malignancies, such as leukemia and lymphoma. The causative gene, *ATM*, is located on chromosome arm 11q, and the carrier frequency of mutations is estimated at 1%.⁴² A study of female relatives of known *ATM* heterozygotes found that carriers had a four-fold greater risk of breast cancer than did noncarriers.⁴³ A previous study had also indicated that the risk of breast cancer in female heterozygotes may be further increased by exposure to ionizing radiation.⁴⁴ This issue remains controversial, however, as other studies have not demonstrated a link between *ATM* heterozygosity and an elevated breast cancer risk.⁴⁵ Further research is needed to clarify the clinical implications associated with *ATM* mutations.

Cowden Syndrome

Cowden syndrome is a rare autosomal dominant condition characterized by multiple hamartomatous lesions and an increased risk of early-onset breast cancer and thyroid cancer.⁴⁶ The hamartomas seen in association with this condition are present in skin, oral mucosa, breast, and intestine. The mucocutaneous hamartomas include papillomas of the lips and mucous membranes, acral keratoses of the skin, and rough-surfaced facial papules called *trichilemmomas*. The majority of individuals affected with Cowden syndrome develop skin lesions by age 20. Breast cancer may affect 25% to 50% of females with Cowden syndrome. Many of these women will be diagnosed premenopausally, and the majority do not appear to have a family history of breast cancer.⁴⁷ Schrager et al. noted that the malignant tumors are usually ductal in origin and are often surrounded by densely collagenized hamartomatous lesions.⁴⁷ Also, an increased incidence of bilateral disease has been observed for benign and malignant conditions.⁴⁷ For example, the benign conditions associated with Cowden syndrome, which may occur

in up to 75% of affected women, include ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, fibroadenomas, and fibrocystic changes.^{46,47} Management of breast cancer risk includes monthly breast self-examination, annual breast examinations by a physician, and mammography at age 30 or 5 years earlier than the youngest age of breast cancer onset in the family.⁴⁶ Another common feature of Cowden syndrome is nonmedullary thyroid cancer, which may be observed in up to 10% of individuals with this disorder.⁴⁶ In addition, more than one-half of those affected with Cowden syndrome have follicular adenomas or multinodular goiter of the thyroid.⁴⁶ Germ-line mutations in the *PTEN* (phosphatase and tensin homologue) gene have been identified in patients with Cowden syndrome, and predictive testing may be available for some individuals if a mutation is identified.^{46,48} Because of the complex presentation of this disorder, patients are usually managed by a multidisciplinary team including surgeons, gynecologists, and dermatologists.⁴⁶

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by hamartomatous polyps in the gastrointestinal tract and by mucocutaneous melanin deposits in the buccal mucosa, lips, fingers, and toes. Studies have described an increased risk of both gastrointestinal and extraintestinal cancer associated with this syndrome, including some rare genital tumors.⁴⁹ Although only a limited number of cases have been reported, Boardman et al. observed an excess number of women with Peutz-Jeghers syndrome who were affected with breast cancer, with an average age at diagnosis of 39.⁴⁹ These data were derived from 34 patients in 31 kindreds. A study of 31 patients from 13 families studied at Johns Hopkins University revealed that 15 (48%) of the affected patients developed cancer, of whom 2 developed ductal cancer of the breast at ages 41 and 56.⁵⁰ Thus, in addition to the special surveillance for colon disorders and other associated findings, women with this syndrome need, at a minimum, routine surveillance for breast cancer. Genetic studies have shown that many, but not all, Peutz-Jeghers syndrome families are characterized by mutations at the chromosome locus 19p13.3⁵¹; germ-line mutations in *STK11*, a serine/threonine kinase gene, have been identified in several affected individuals.⁵²

Muir-Torre Syndrome

Muir-Torre syndrome is another rare autosomal dominant condition that is considered to be a variant of hereditary nonpolyposis colorectal cancer (HNPCC). The hallmark of this condition is multiple sebaceous gland and skin tumors, including keratoacanthomas and basal cell carcinomas. These cutaneous manifestations are typically seen in associ-

ation with tumors of the small and large bowel. In addition, tumors of the larynx, stomach, endometrium, kidney, bladder, ovaries, and breast are observed. One review noted that the world literature contains 162 cases of Muir-Torre syndrome, with 316 internal malignancies documented.⁵³ Ninety percent of these were gastrointestinal, urogenital, or breast cancers. Overall, the average age of diagnosis of Muir-Torre syndrome is 55 years, and the diagnosis is usually based on dermatologic findings.⁵⁴ Little specific information is available to characterize further the nature of the breast cancers in affected individuals. Mutations in the DNA mismatch-repair genes *MSH2* and *MLH1*, the major genes implicated in HNPCC, are associated with this condition; thus, predictive testing may be possible for some families.^{55,56} As with other complex cancer predisposition syndromes, specific management plans have been developed, and affected or at-risk individuals are often followed by a multidisciplinary team.^{54,57}

GENETIC COUNSELING PROCESS

Genetic counseling for high-risk individuals is critical, especially when genetic testing is an option. In the latter case, both pretest and posttest counseling are important because of the complexities in test result interpretation and medical management options and the potential emotional ramifications of test results.⁵⁸ The process of genetic counseling, as outlined in Fig. 2, may help individuals to make informed decisions about whether they would like to pursue testing based on the potential benefits, risks, and limitations. In addition, they are also afforded an opportunity to contemplate how the information may impact them and their families.

Initial, or pretest, genetic counseling sessions involve a detailed review of the patient's family and medical history. The family history may be conveniently recorded in the form of a pedigree and updated as needed. Pedigrees recorded for the purpose of cancer risk assessment should include information about maternal and paternal relatives, preferably covering three generations. With respect to cancer history, the practitioner should record and document, where possible, all cancer or precancer diagnoses, ages of the individuals at diagnosis, laterality, treatment, and history of prophylactic surgery. Relevant environmental and exposure history is also important to note, as is ethnic ancestry. In addition, current ages of living family members, ages and causes of death of deceased individuals, and other chronic medical conditions of unaffected and affected individuals should be indicated on the pedigree. Analysis of the pedigree for hallmark features of hereditary cancer provides the basis for an accurate risk assessment.

Many patients overestimate the contribution of single gene mutations to breast and ovarian cancer, and many unaffected women in particular overestimate their risk of developing these cancers.^{59,60} Thus, it is valuable to tell patients whether the features of the family history are suggestive of hereditary

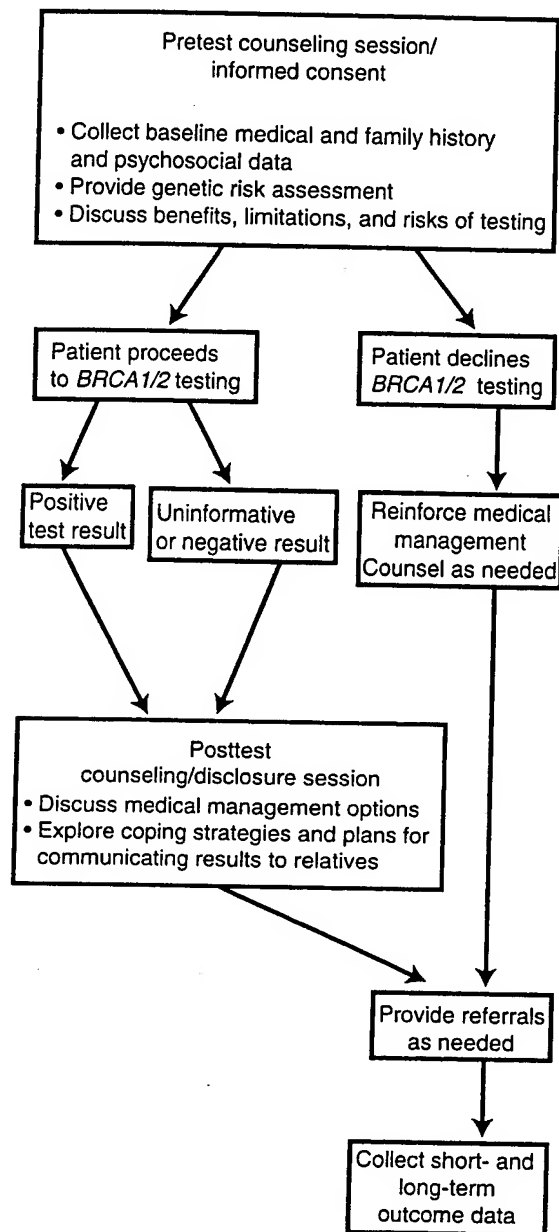


FIG. 2. Flow diagram depicting the process of genetic counseling.

breast cancer, and, if so, what the likelihood is that testing will provide a clinically meaningful result. For some families, a sizable difference may exist between the likelihood that the cancers in the family are hereditary and the probability that a mutation will be detected.⁶¹ Although various models and methods are available for evaluating the chance that testing for the two major breast cancer genes, *BRCA1* and *BRCA2*, will yield a positive result, these data need to be interpreted in the context of a specific pedigree. Patients also must weigh the financial cost of testing if this service is not offered as part of a research protocol. A discussion of inheritance patterns (usually autosomal dominance) is also very

although three *BRCA1* and *BRCA2* mutations account for the majority of alterations found in individuals of Ashkenazi Jewish descent, novel mutations have been reported that would require further analysis to detect.²⁵

Testing can have many possible outcomes. The most unambiguous results are either "true positives" or "true negatives." "True positive" results refer to nonsense or frameshift mutations (due to deletions or insertions) that lead to protein truncation. In addition, some alterations, including some missense mutations, are known to be deleterious based on functional assays or RNA studies.⁷³⁻⁷⁵ A catalogue of reported mutations is also available on-line, which, together with published reports, reveals that some mutations have been identified in numerous high-risk families.^{23,25,76} In the future, it may be possible to correlate cancer risks with specific mutations; at present, however, such data are too preliminary to be useful in clinical counseling. "True negative" results refer to the case in which an individual tests negative for the mutation identified in his or her family, usually in a close relative. The standard practice is to test these relatives only for the presence or absence of the familial mutation; the exception is individuals of Ashkenazi Jewish descent, for whom all three founder mutations should be analyzed, given the high background frequency of these mutations.⁵ The finding of a "true negative" result has significant implications, as these individuals usually can be reassured that their cancer risks are approximately the same as those of other individuals in the general population, and therefore only routine screening is warranted.

The most difficult results to interpret are those in which no deleterious mutations are identified after full testing, or those in which an alteration of uncertain clinical significance is found. If an affected high-risk individual is the first to be tested in the family, a negative result could arise for a number of reasons; for example, (a) a mutation could be present (e.g., in a regulatory region) but is not detectable by available methods; (b) another gene that is rare or not yet isolated could be implicated; or (c) the individual tested could have developed sporadic cancer. In many cases, distinguishing which of these possibilities accounts for the negative finding is difficult. Also, genetic variants, termed *mutations of uncertain clinical significance*, may be found that do not overtly affect the gene's protein product. Such alterations are usually missense mutations (single base pair changes). Missense mutations may be presumed to be of little clinical consequence if they occur in noncritical domains of the gene, result in a single amino acid's being substituted with a similar amino acid, or occur in conjunction with known deleterious mutations. However, in the absence of functional tests or multiple segregation analyses, these determinations remain only speculative. Proper interpretation of test results is critical, because individuals may use this information, interpreted in the context of their medical and family histories, to make significant decisions regarding medical management.

PSYCHOSOCIAL ISSUES

Patient Decision Making about Genetic Testing

To make an informed decision about genetic testing, patients must be educated about the benefits, limitations, and risks of testing as described previously. Given the complexities and challenges inherent in this decision, the fact that preliminary data suggest that many high-risk individuals choose not to learn their genetic status is not surprising. In a prospective cohort study of *BRCA1* testing in 279 members of families with hereditary breast and ovarian cancer,⁶³ only 43% decided to receive their test results. Individuals with health insurance, those who had a greater number of affected relatives, and those who were more knowledgeable about breast cancer genetics were more likely to participate. Reasons cited for wanting the testing included the desire to learn about their children's risks, the wish to be reassured, and the need to make decisions about screening and surgery. Reasons for not wanting testing included possible insurance discrimination, potential emotional effects on self and family, and concerns about test accuracy. In addition to these factors, evidence exists that psychological distress motivates desire for genetic testing for breast cancer susceptibility.⁷⁷ This finding is worrisome, because it suggests that the individuals most likely to request testing may be more psychologically vulnerable. These data underscore the importance of discussing these psychosocial aspects of the testing decision with patients, in addition to addressing genetic and medical issues.

Disclosure of Genetic Test Results

With the identification of the major breast cancer susceptibility genes, early reports warned of the potential for adverse psychosocial consequences of disclosure of genetic information.^{58,78} Several controlled investigations of the psychosocial impact of *BRCA1* testing have now been initiated, and data are available to address this question.

The first of these studies focused on the psychosocial effects of testing in a large hereditary breast cancer kindred in Utah. The study protocol and measures were described previously.⁷⁹ An analysis of the first 60 women who received *BRCA1* mutation test results found no evidence of significant adverse psychological effects.⁸⁰ No significant change was seen in the level of general anxiety reported by carriers. Among noncarriers, a small but significant decline in anxiety was noted. However, on a measure of stress responses specific to genetic testing, one group showed significantly higher levels of stress compared with the other participants. Specifically, women with no history of cancer or prophylactic surgery reported higher levels of stress after genetic testing. In contrast, mutation carriers who had already experienced cancer or prophylactic surgery showed no more stress than noncarriers. Overall, however, levels of stress responses were not substantially elevated above the norm.

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important. This risk should be contrasted with the cancer risks associated with mutations in predisposing genes, and an individualized explanation of available medical management options should be given.

Another important aspect of pretest counseling is the review of the possible benefits, risks, and limitations of genetic testing. Although no individual can imagine fully how he or she might react on learning a test result, engaging in this discussion beforehand can at least begin to prepare individuals for different responses and enable them to mobilize coping, support, and informational resources ahead of time.

Potential benefits of testing include the reduction of uncertainty due to increased knowledge. In addition, results may help facilitate more informed decision making about medical options, including prophylactic surgery. Although such surgery may be undertaken by women who have never had a diagnosis of cancer, data regarding the risk of ipsilateral and contralateral breast cancers in *BRCA1* and *BRCA2* carriers could potentially impact the surgical decision making of high-risk patients newly diagnosed with breast cancer who choose to learn their genetic status preoperatively.⁶² Frequently, the choice to be tested may also be motivated by a desire to obtain information for other family members. In some instances, the medical implications for cancer patients who are the first in their families to pursue testing may not be highly significant, but the knowledge obtained for relatives could be substantial.

Limitations of testing include the possibility that results may not be informative. Even when test results are positive, broad or uncertain ranges of cancer risks combined with the lack of long-term outcome data regarding management strategies may complicate medical decision making. Although no substantial physical risks are associated with genetic testing, the psychosocial risks may be considerable. A common reason for declining genetic testing is the fear of genetic discrimination in the areas of health and life insurance, and employment.⁶³ The existing federal legislation does not apply to all individuals, and the provisions that are available usually apply to health insurance but not life insurance. Therefore, even those who do choose to obtain test results often exercise caution about how and with whom the information is shared.

Although studies have not demonstrated significant adverse emotional effects of testing, as described in the section Psychosocial Issues, carriers normally experience some level of distress, anxiety, or sadness.⁶⁴ Although many individuals pursue testing for the sake of obtaining information for family members,⁶³ the decision to disseminate one's test results and the ensuing ramifications can cause strain among relatives. It is not uncommon for those with true negative results to feel a combination of relief and "survivor guilt" for being spared a burden that other relatives may experience. In addition, the role of information gatekeeper may be overwhelming for some individuals as they try to attend also to their own needs for support. Registry-based

and clinic-based studies of large families have demonstrated that most individuals, carriers and noncarriers, do opt to share their results with relatives at risk⁶⁵; however, a provider cannot understand or know the multitude of dynamics within families that may result in either open or impeded communication regarding risk.⁶⁶ Nevertheless, the genetic counselor should tell patients what the implications to family members may be, identify individuals at risk based on the pedigree structure, and encourage patients to share this information with their relatives.⁶⁷

Thus, because of the possible significance of these issues to patients, an integral part of the informed-consent process is discussion of these issues before genetic testing. Posttest genetic counseling provides an opportunity to review pertinent information and may also serve to help individuals begin to assimilate their results. Specially trained genetic counselors and nurses are now available in most areas of the country who can provide these services to interested patients, often in combination with a multidisciplinary team of professionals, such as oncologists, surgeons, geneticists, and psychologists.

ISSUES IN TEST RESULT INTERPRETATION

Regardless of which hereditary breast cancer syndrome is suspected within a family, the degree to which testing will be informative is always maximized by first testing the individual in the family who is most likely to carry a mutation (i.e., usually a woman with breast or ovarian cancer diagnosed at a young age). The most complete and most expensive method of gene testing is direct sequencing of exons and adjacent noncoding introns. This method is thought to have the highest degree of sensitivity and specificity. For example, a commercial laboratory has estimated that the sensitivity of *BRCA1* and *BRCA2* sequencing is greater than 98%.⁶⁸ However, because sequencing cannot detect deletions of complete exons or genes or some errors in RNA processing, up to 15% of mutations in *BRCA1* and *BRCA2* may be missed. This estimate is based in part on findings from families showing evidence for linkage to *BRCA1* and *BRCA2* in which no deleterious mutation could be identified.^{69,70} Other assays for full gene analysis are available that vary in sensitivity (e.g., conformation-sensitive gel electrophoresis).⁷¹ To date, no systematic, blinded studies have been conducted to directly compare these alternative methods of testing for sensitivity and specificity.

Techniques designed to identify specific mutations are very accurate. These include allele-specific oligonucleotide (ASO) and allele-specific polymerase chain reaction (PCR) assays and fluorogenic PCR allelic discrimination assays.^{13,72} These methods may be used to test for familial mutations or to test for panels of common mutations. However, when a first attempt is made to identify a mutation in a family, negative test results from partial testing methods such as these must be considered inconclusive. For example,

A second prospective cohort study focused on several extended families in a hereditary breast cancer registry.⁶³ The study sample included 46 carriers of *BRCA1* mutations, 50 noncarriers, and 44 individuals who declined *BRCA1* testing. At baseline and 1-month follow-up, all three groups scored in the normal ranges on measures of depression and functional health status. Noncarriers of *BRCA1* mutations exhibited significant decreases in depressive symptoms and role impairment and marginally significant decreases in sexual impairment, compared with carriers and those who declined testing. Carriers and those who declined testing did not exhibit changes in any of these distress outcomes. Six-month follow-up data from this cohort suggest that this pattern of responses is maintained over time.⁸¹

Although these two initial reports do not provide evidence for significant or pervasive adverse psychological effects of *BRCA1* testing, caution is warranted in generalizing these findings to other populations and settings. Participants in these studies were members of high-risk families in hereditary cancer registries, many of whom were involved in prior cancer genetics studies. These families had been included in the registries because of their unusually high cancer rates. Because study participants had witnessed cancer in many close family members, their emotional responses may have been blunted. In addition, most unaffected individuals in these high-risk families reported before testing that they expected to be mutation carriers. Thus, receiving a positive test result may have confirmed what they believed to be true all along. In some cases, worrying about the possibility of being a mutation carrier may be no less distressing than having that belief confirmed. Individuals who have less significant family histories, and who do not expect to receive positive results, may be more vulnerable to adverse psychological sequelae of *BRCA1* testing. All individuals in these studies were white (all of the Utah subjects were Mormon), and most had a high school education. In addition, all testing was provided free of charge as part of research protocols with extensive education and counseling.

Although these initial studies have not found evidence for significant psychological morbidity, emotional responses to testing may vary widely. One study examined the use of a brief precounseling assessment to identify individuals at risk for adverse psychological effects of genetic testing for breast cancer susceptibility.⁸² The results showed that the presence of cancer-related stress symptoms was highly predictive of subsequent depression in a subgroup of hereditary breast cancer family members. However, contrary to predictions, these adverse effects were seen primarily in individuals who were offered but declined genetic counseling and testing. These results suggest that members of families in which a mutation is identified who decline genetic testing should also be monitored for adverse effects, especially if they manifest cancer-related stress symptoms. The development of depression in these individuals may be minimized by their participation in genetics education and counseling programs, even if they ultimately decline to be tested.

Medical Decision Making

For *BRCA1* and *BRCA2* testing to lead to the anticipated reductions in breast and ovarian cancer mortality, mutation carriers must adopt recommendations for intensive and frequent surveillance. However, relatively less attention has been focused on understanding psychological issues in medical decision making in these high-risk patients. Data from the cohort study of hereditary breast cancer family members suggest that adherence to screening regimens is suboptimal.⁸¹ Only 60% of eligible carriers had the recommended mammograms during the 6 months after testing, and fewer than 10% had transvaginal ultrasound or the serum tumor marker CA-125.

In lieu of participating in frequent and intensive surveillance, many high-risk women seek counseling about whether to obtain prophylactic surgery. In the cohort study described above, among unaffected female *BRCA1* carriers, 18% intended to obtain prophylactic mastectomies and 33% intended to obtain prophylactic oophorectomies.⁶³ Among carriers of cancer-predisposing genes, prophylactic surgery may have psychological benefits, such as the reduction of chronic worry.⁸³ However, such procedures also carry psychological risks.⁸⁴ One study suggested that breast cancer-related distress may also influence prophylactic mastectomy decisions.⁸⁵ In this study, women were presented with vignettes that described a woman at high risk for breast cancer who was deciding whether to obtain a prophylactic mastectomy or to have close breast cancer follow-up. Women were asked to indicate what their choice would be in that situation. Women who had higher levels of perceived personal risk and higher levels of breast cancer worries were significantly more likely to select prophylactic mastectomy over close follow-up. Younger women and women selecting prophylactic mastectomy reported less confidence in their choices.

For women at high risk for breast cancer, another important decision concerns whether to participate in chemoprevention trials. As yet, however, the factors that influence the decisions of high-risk women regarding participation in such trials are poorly understood. One study of recruitment of high-risk women to a breast cancer health promotion trial suggested that the timing of the recommendation may be an important determinant. In this study, women with a higher level of formal education were more likely to participate if they were approached within the first 2 months after the breast cancer diagnosis of a close relative.⁸⁶ Familial polyposis patients also were more likely to participate in a colon cancer chemoprevention program if they had been diagnosed more recently.⁸⁷ During the initial period after a personal cancer diagnosis or diagnosis in a close relative, heightened perceived risk or distress may motivate risk-reduction behaviors, such as participation in a chemoprevention or health promotion trial.

Preliminary data suggest that reproductive plans and choices may also be altered by genetic testing for breast cancer susceptibility. In a survey of 56 women aged 40 years and younger who had a family history of breast cancer, 22%

reported that they would be less likely to have children if they tested positive for a *BRCA1* mutation, and 17% reported being uncertain as to whether they would complete a pregnancy under these circumstances.⁸⁸

The findings reviewed in this section suggest that psychological support may be important for high-risk women faced with difficult medical management decisions. Psychosocial interventions for women at high risk of breast cancer have been reviewed elsewhere.^{89,90} Research conducted with breast cancer patients suggests that training in structured decision-making strategies can enhance medical decision making and psychological adjustment.⁹¹ These strategies, developed and evaluated in the nursing literature, could be adapted easily to assist high-risk women in deciding whether to undergo prophylactic surgery or to participate in chemoprevention trials. Although such educational approaches may be sufficient for some patients, others may require referral to more formal psychological counseling services. Thus, health care providers who may lack the time or the training to deliver psychosocial counseling should establish mechanisms for referral of their patients to psychiatrists, psychologists, or other mental health professionals.

MEDICAL MANAGEMENT OF HIGH-RISK INDIVIDUALS

At present, few proven methods exist for cancer screening or prevention for high-risk women or those with an inherited susceptibility to cancer. Studies are currently under way that address the impact of some of these strategies on the cancer risk of mutation carriers. High-risk women must fully understand their various cancer screening and prevention options so that they can make informed decisions about their medical care. These options are outlined in the following paragraphs.

Breast Cancer

Screening Options

Little data exist to document the benefit of screening interventions in mutation carriers or other high-risk individuals. The current breast cancer screening guidelines for women with a known inherited susceptibility to cancer who do not elect to have prophylactic surgery include monthly breast self-examinations, semiannual or annual clinician-performed breast examinations beginning at age 25 to 35, and annual mammograms beginning at age 25 to 35.⁹² Controversy exists about the age at which mammographic screening should commence and the intervals at which it should be repeated; most of this controversy relates to the use of mammography in women younger than 40. Although the risk exists of false-positive results or false reassurance from neg-

ative results, particularly in this age group, some series have demonstrated the value of screening mammography in women younger than 40.^{93,94} In addition, preliminary evidence suggests that the mammographic appearance of *BRCA1*-associated breast cancers is similar to that of sporadic cancers.⁹⁵ Because of concerns that *BRCA* tumors may have a faster growth rate than sporadic tumors, and to allay patient anxiety, some clinicians recommend mammography every 6 months to carriers beginning at age 25 to 35.⁹⁶ However, because of theoretical concerns about the role of mammography in breast carcinogenesis in carriers⁹⁷⁻⁹⁸ and the lack of data, the use of mammography more than once per year is generally discouraged in the absence of a specific indication. Most experts, however, believe that the benefit of early detection with annual mammograms beginning at age 25 to 35 outweighs the potential for adverse effects.^{92,99} Clinical trials of other imaging techniques, such as magnetic resonance imaging, may lead to the development of more sensitive methods of early detection without the associated radiation exposure.

For women at moderate risk of breast cancer, monthly breast self-examination and semiannual or annual clinician-performed breast examinations are recommended. Despite the controversy about the benefit of screening mammography for women between the ages of 40 and 49, annual mammograms beginning at age 40 in this moderate-risk group are recommended.

Prevention Options

Prophylactic Mastectomy

A study by Hartmann et al. evaluated the efficacy of prophylactic mastectomy in women with a family history of breast cancer.¹⁰⁰ This study included more than 600 women who were either at moderate or high risk of breast cancer on the basis of their family histories. Women with any family history of breast cancer were considered at moderate risk. Approximately two-thirds of the women included in this moderate-risk group had at least one first-degree relative with breast cancer. The definition of high risk in this study was quite broad, and other data²⁴ suggest that, at most, 10% of these women would be carriers of *BRCA1* mutations.

For the 425 moderate-risk women, the investigators used the Gail model to predict the expected numbers of cases of breast cancer. With a median follow-up of 14 years, the Gail model predicted 37 cases of breast cancer, and four were seen. This highly statistically significant difference translated into a 90% reduction in the incidence of breast cancer. To evaluate the efficacy of prophylactic mastectomy in high-risk women, their untreated sisters served as controls. This approach demonstrated that prophylactic mastectomy reduced the risk of breast cancer in high-risk women by at least 90%. In addition, breast cancer-related mortality was reduced by at least 81% in the high-risk group and by 100%

in the moderate-risk group. This study demonstrated that prophylactic mastectomy significantly reduced breast cancer incidence in women at increased risk for this disease. Women entered in this study received both prophylactic subcutaneous and total mastectomy. Subcutaneous mastectomy is no longer considered the procedure of choice due to the fact that a significant amount of breast tissue is found in the nipple-areolar complex. With the availability of improved surgical techniques, including skin-sparing mastectomies and newer methods of reconstruction, most surgeons now recommend prophylactic total mastectomy (see Chapter 18).

Schrag et al. used decision-analysis tools to predict the benefits of prophylactic surgery in mutation carriers.¹⁰¹ They modeled an 85% reduction in risk of breast cancer for carriers undergoing prophylactic mastectomy and found that a 30-year-old female mutation carrier would gain 2.9 to 5.3 years of life expectancy from this surgery. Although there is reason to be optimistic about the benefits of prophylactic mastectomy in *BRCA1* and *BRCA2* mutation carriers, currently published studies have not specifically addressed this issue. Thus, caution should be used when extrapolating results of these studies to mutation carriers. Studies focusing on mutation carriers are under way and should provide clearer answers on the efficacy of this approach in this patient population.

Prophylactic Oophorectomy

In individuals with hereditary breast cancer, one study demonstrated that healthy *BRCA1* carriers who had undergone prophylactic bilateral oophorectomy had a significant reduction in their risk of breast cancer.¹⁰² Overall, the risk of breast cancer was reduced by more than 70% in those undergoing prophylactic oophorectomy. Thus, in *BRCA1* and *BRCA2* carriers, prophylactic oophorectomy likely reduces the risk not only of ovarian cancer but also of breast cancer. No data exist on the impact of this procedure in other moderate-risk or high-risk women.

Chemoprevention

The Breast Cancer Prevention Trial randomized more than 13,000 healthy high-risk women into groups receiving 5 years of tamoxifen (tamoxifen citrate) therapy or placebo.¹⁰³ Eligible women included any woman age 60 or older, those between the ages of 35 and 59 with a predicted 5-year risk of breast cancer of 1.66% or higher, and anyone older than age 35 with lobular carcinoma *in situ*. Of the study participants, 56% had one first-degree relative with breast cancer, 16% had two affected first-degree relatives, and 3% had three affected first-degree relatives. With a median follow-up of 4.5 years, tamoxifen was found to halve the risk of invasive estrogen receptor-positive tumors and noninvasive breast cancer. No reduction in risk of estrogen receptor-negative tumors was seen. The reduction in breast cancer risk was

seen for all family history constellations and all age groups of women, as well as those with lobular carcinoma *in situ* and atypical ductal hyperplasia. Based on the results of this study, the Food and Drug Administration approved the use of tamoxifen for reducing the incidence of breast cancer in women at high risk for developing the disease. In contrast to the Breast Cancer Prevention Trial, the Royal Marsden Hospital tamoxifen randomized chemoprevention trial failed to demonstrate a decreased incidence of breast cancer in the tamoxifen group.¹⁰⁴ In this study, a total of 2,471 women with at least one first-degree relative younger than age 50 with breast cancer were randomized into treatment and non-treatment groups. Of note, a significant proportion of women took hormone replacement therapy at some point during this trial. The disparity of results seen in these two studies has not yet been fully explained. It has been postulated that some of the differences may be due to the fact that tamoxifen is not effective as a chemoprevention agent in patients with familial or hereditary breast cancer. The Breast Cancer Prevention Trial is currently performing a subgroup analysis and is genotyping a subset of participants to determine the effectiveness of tamoxifen in preventing breast cancer in *BRCA1* and *BRCA2* mutation carriers. Thus, at present, a reasonable approach is to consider the use of tamoxifen for breast cancer prevention in women who fit the eligibility criteria of the study and to exercise greater caution when considering this therapy for those with an inherited susceptibility to breast cancer. The benefits in the latter group will become clearer when the results of the subgroup analysis are available. In general, health care providers are advised to carefully evaluate the benefits and risks for any individual patient before prescribing this drug.

Other chemoprevention trials are under way. These include the Study of Tamoxifen and Raloxifene (STAR) trial, in which postmenopausal moderate-risk and high-risk women will be randomized to treatment with tamoxifen or raloxifene (raloxifene hydrochloride), a selective estrogen-receptor modulator. In addition, trials in known mutation carriers are also planned. Chemoprevention is discussed in detail in Chapter 19.

Hormone Replacement Therapy and Other Options

Postmenopausal women generally consider taking hormone replacement therapy (HRT) to reduce their risk of cardiovascular disease and osteoporosis and to treat postmenopausal symptoms. However, long-term use of HRT in women in the general population increases the risk of breast cancer (relative risk, 1.2–1.5).^{105,106} Concern exists that this risk would be magnified in women with a family history of breast cancer and in those with *BRCA1* or *BRCA2* mutations. Several studies have addressed whether family history influences the risk of breast cancer in users of HRT. These studies have varied from showing no effect to finding a 3.4-fold excess risk of breast cancer in those with a positive fam-

ily history.¹⁰⁷ Little information exists on the effect of HRT in women who are *BRCA1* or *BRCA2* carriers. Thus, the decision to take HRT for protection against heart and bone disease and for relief from menopausal symptoms is often a difficult one both for women with a positive family history of breast cancer and for those with *BRCA1* or *BRCA2* mutations. This issue may be of particular concern to *BRCA1* or *BRCA2* carriers who are considering or have undergone prophylactic oophorectomy and thus are faced with the consequences of premature menopause. At present, little information is available to guide patients and their physicians who are considering this option. In general, the recommendation is that *BRCA1* or *BRCA2* carriers avoid this therapy and that women with a low to moderate risk of breast cancer based on family history carefully consider the risk to benefit ratio of such treatment.

Several other treatment options are now available to reduce a woman's risk of cardiac disease and osteoporotic fracture. These include the selective estrogen-receptor modulators tamoxifen and raloxifene. Tamoxifen and raloxifene lower both total cholesterol and low-density-lipoprotein cholesterol.^{108,109} and tamoxifen may reduce the risk of coronary heart disease.^{110,111} Tamoxifen has been demonstrated to increase bone mineral density in the lumbar spine both in healthy women¹¹² and in breast cancer patients¹¹³ and to decrease hip and Colles' fractures in healthy women.¹⁰³ Randomized trials have demonstrated that raloxifene is effective at preventing bone loss, although neither raloxifene nor tamoxifen is as potent as HRT.^{109,114} Like tamoxifen, raloxifene appears to have antiestrogenic activity at the level of the breast. A combined analysis of placebo-controlled trials in healthy postmenopausal women indicated that women receiving raloxifene had a 55% reduction in risk of developing invasive breast cancer.¹¹⁵ Thus, tamoxifen and raloxifene may be useful alternatives to HRT in this patient population. Not only do they reduce the risk of osteoporosis and possibly heart disease, but they also appear to protect against breast cancer. Unfortunately, both of these agents tend to worsen hot flashes and provide little if any relief from other postmenopausal symptoms, such as vaginal dryness. In addition to the selective estrogen-receptor modulators, bisphosphonates and calcitonin can be used safely in this patient population to prevent or treat osteoporosis.

Individuals with documented *BRCA1* or *BRCA2* mutations also face increased risks of other cancers, including ovarian cancer, prostate cancer, and possibly colon cancer. The screening and prevention options for these malignancies are outlined in the following paragraphs.

Ovarian Cancer

Screening Options

For mutation carriers who have not had prophylactic oophorectomy, semiannual or annual transvaginal ultrasonography with color Doppler and CA-125 is recom-

mended beginning at age 25 to 35.⁹² The benefits of these screening options for mutation carriers are unknown. In the general population, these measures have not been proven very effective. However, these measures may possibly have a higher predictive value in mutation carriers, given the high incidence of ovarian cancer in this patient group.

Prevention Options

Prophylactic Oophorectomy

Prophylactic oophorectomy should be considered in mutation carriers; however, the efficacy of such an approach in high-risk women and mutation carriers is unknown. Clearly, a residual risk of primary peritoneal carcinomatosis exists. Two studies shed some light on this risk. Of the 324 women from the Gilda Radner Familial Ovarian Cancer Registry who had undergone prophylactic bilateral oophorectomy, 6 (2%) developed primary peritoneal carcinomatosis 1 to 27 years after this procedure.¹¹⁶ A second study found that members of high-risk families who had undergone prophylactic oophorectomy had a 13-fold excess risk of "ovarian" cancer as compared with a 24-fold excess risk of ovarian cancer in those family members who had not had prophylactic surgery.¹¹⁷ Thus, these studies suggest that prophylactic surgery reduces the risk of ovarian cancer in members of high-risk families, but that residual risks remain. Further research is under way addressing the impact of this surgery in known mutation carriers.

Chemoprevention

Oral contraceptive use is known to decrease the risk of ovarian cancer in the general population.¹¹⁸ As discussed in the section on Cancer Risk Modifiers, one case-control study suggested that oral contraceptive use also significantly reduced the risk of ovarian cancer in *BRCA1* and *BRCA2* carriers.³⁵ However, some concern exists that oral contraceptive use may increase the risk of breast cancer in mutation carriers.³⁶ Given the limited knowledge, mutation carriers face a difficult decision as they balance the potential risks and benefits of the pill.

Prostate Cancer

Typically, the age of onset of prostate cancer in mutation carriers is similar to that in individuals with sporadic disease. Thus, the screening recommendations are the same as those for the general population and include annual rectal examination and prostate-specific antigen testing beginning at age 50.

Colon Cancer

Individuals with a *BRCA1* or *BRCA2* mutation should follow the screening guidelines for the general population.

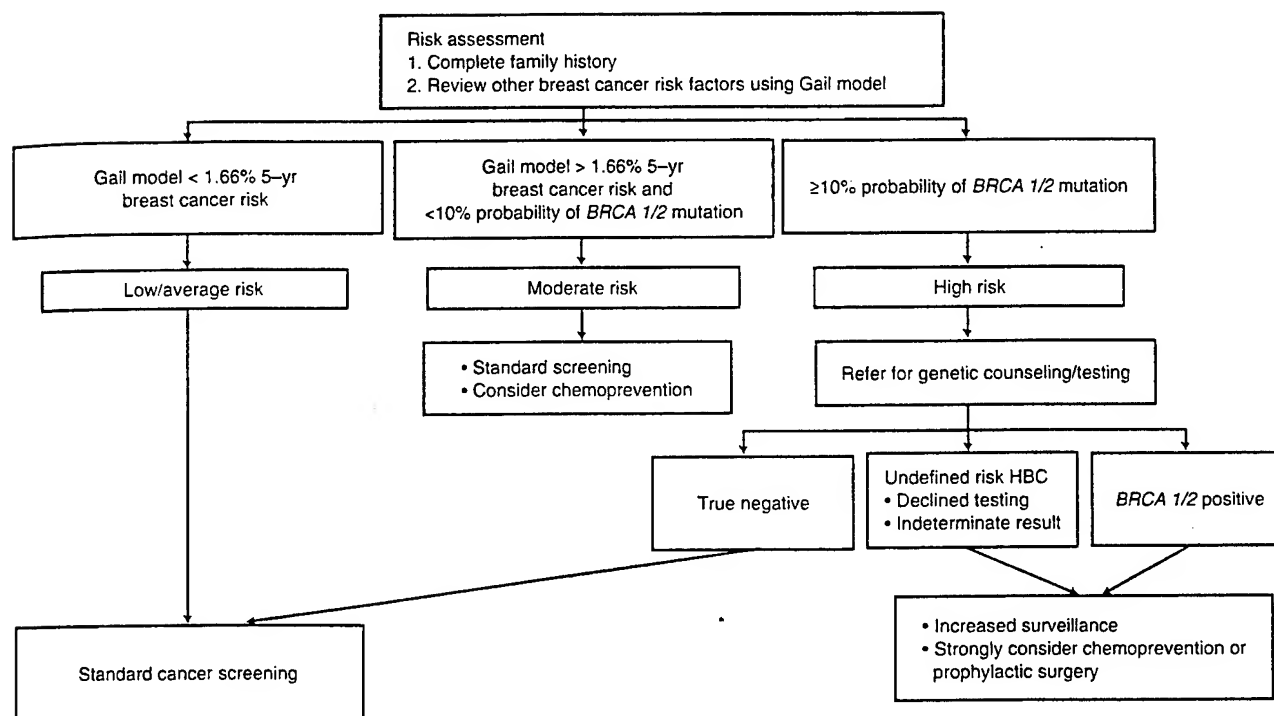


FIG. 3. Flow diagram depicting the process of risk evaluation and management of women with a family history of breast cancer. HBC, hereditary breast cancer.

These include fecal occult blood test annually and flexible sigmoidoscopy or colonoscopy every 3 to 5 years beginning at age 50.

Individualizing Screening and Prevention Programs

High-risk women, particularly those found to be mutation carriers, must understand that no proven means of cancer prevention or screening exist. Thus, each woman should be encouraged to take the time to weigh fully the implications of different management approaches before deciding on a particular plan. Not infrequently, an individual's approach changes over time. For example, a young woman with a *BRCA1* mutation may choose surveillance for ovarian cancer if she has not yet completed childbearing. Once her family is complete, she may then wish to consider prophylactic surgery. High-risk women should be strongly encouraged to participate in clinical trials addressing the efficacy of cancer screening and prevention strategies.

SUMMARY

Most individuals with a family history of breast cancer have a familial rather than hereditary basis to their disease. Among women with hereditary breast cancer, *BRCA1* and *BRCA2* mutations account for the majority of cases. Muta-

tions in these genes are associated with a significantly elevated risk of early-onset breast and ovarian cancer. In addition, other cancers may be seen with an increased frequency in mutation carriers. Models based on cancer history, family history, and ethnic background are available to guide clinicians in estimating the likelihood that an individual harbors a risk-conferring mutation. Due to the complexities involved in decision making about genetic testing and medical management, genetic counseling is critical before testing is carried out. The process of risk evaluation and management for women with a family history of breast cancer is outlined in Fig. 3. Studies on genetic and environmental cancer risk modifiers, genotype-phenotype correlations, and the impact of cancer screening and prevention options are under way and will continue to provide further insight into the features and management of high-risk individuals.

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Table 1
Medical Management Options for BRCA1/2 Mutation Carriers

Cancer Type	Provisional Guideline
Breast Cancer	Instruction and practice in monthly breast self-exam (BSE) by age 18–21 Clinician performed exam every 6–12 mo and annual mammogram beginning between ages 25–35 Consideration of chemoprevention trial Consideration of prophylactic mastectomy
Ovarian Cancer	CA-125 levels and transvaginal ultrasound with color Doppler every 6–12 mo beginning between ages 25–35 Consideration of oral contraceptive use Consideration of prophylactic oophorectomy
Prostate Cancer	Rectal exam and PSA levels annually beginning at age 50
Colon Cancer	Fecal occult blood test annually and flexible sigmoidoscopy every 3–5 yr beginning at age 50
Other sites (e.g., cervix, skin, etc.)	Education about risk; standard age-appropriate guidelines

^aModified from ref. 13.

rian cancer risk (15), it is unknown whether this is true also for women with BRCA1/2 mutations. It is likely that randomized trials of chemopreventive agents will become available to BRCA1/2 mutation carriers in the future.

The other method for potential risk reduction is surgery to remove the at-risk tissue or organ, such as prophylactic mastectomy or oophorectomy. Although these surgeries are thought to reduce the risk of developing breast and ovarian cancer (16), they do not eliminate the risk (13). The decision to undergo preventive surgery may also raise difficult questions regarding how a woman will obtain subsequent screening and how she will deal with the nebulous answers about the advisability of hormone-replacement therapy. Nevertheless, it is possible that women who opt for these procedures may obtain a decrease in anxiety, which enables them to enhance their quality of life. However, further research on the psychological benefits and costs of prophylactic surgery is needed.

2.6. Follow-up After Testing

Except in unusual circumstances, results of genetic testing are disclosed in person, at which time the clinician must balance the patient's desire for information as well as the importance of providing supportive counseling. Pertinent information about cancer risks, management options, and plans for communicating information are reviewed. When appropriate, referrals are made to specialists including oncologists and psychologists. For many patients, supplementing this session with written material and at least one follow-up phone call can serve to reinforce the information, answer questions, and provide further support as they begin to assimilate and accept the implications of their results.

3. EMPIRICAL RESEARCH ON GENETIC TESTING FOR CANCER SUSCEPTIBILITY

3.1. Patient Decision-Making About Testing

As described above, to make informed decisions about genetic testing, patients must weigh the complex information about the benefits, limitations, and risks. According to models of consumer behavior, perceptions of the importance of the benefits (or pros) of testing would be expected to enhance intentions to be tested and actual test use, while concerns about the limitations and risks (or cons) should diminish intentions and hinder testing behavior. These models assume a "rational" process of decision-making in which an individual chooses the option which maximizes "expected utility"—or, in other words, the option for which he/she anticipates a higher likelihood of positive outcomes relative to negative outcomes.

The predictors of BRCA1 gene testing decisions were evaluated in a prospective cohort study of male and female members of hereditary breast-ovarian cancer (HBOC) families who were offered free BRCA1 testing (4). Of 279 individuals, 43% decided to receive BRCA1 test results. It should be noted, however, that because testing was offered free of charge, rates of uptake of commercial testing (costing \$200–\$2400) may actually be lower. Reasons cited for wanting testing (pros) included: to learn about childrens' risks, to be reassured, and to make decisions about screening and surgery. Reasons for not wanting testing (cons) included: possible insurance discrimination, potential emotional effects on self and family, and concerns about test accuracy. Rates of BRCA1 test uptake were significantly greater among females, persons with higher levels of education, those with health insurance, and those who already had been affected with cancer. After controlling for these demographic and medical factors, test uptake was associated positively with knowledge of hereditary cancer and genetic testing and the perceived benefits of testing (pros). However, high levels of perceived limitations and risks (cons) did not deter testing. From a practical standpoint, this finding underscores the importance of emphasizing the limitations and risks of genetic testing to a greater degree in informed consent encounters.

The impact of alternate strategies to enhance informed decision-making for BRCA1 testing was examined in a recent randomized trial (17). In this study, 400 women at low to moderate risk of breast or ovarian cancer were randomized to one of three pre-test education conditions: standard education only (educational approach) or education plus psychosocial counseling (counseling approach) or a wait-list control condition. The counseling approach provided standard education about BRCA1 testing and also asked participants to imagine how they would respond emotionally and behaviorally to positive and negative test results. Knowledge, perceived pros, perceived cons, and intentions were measured prior to education and at 1 mo. Because BRCA1 testing was not available for this population at the time of the study, provision of a blood sample for future testing served as a proxy measure of testing decisions. Compared to the wait-list control condition, both the educational and counseling approaches led to significant increases in knowledge. However, only the counseling approach led to increases in perceived limitations and risks of testing and decreases in perceived benefits. Because participants in the counseling approach had an opportunity to discuss the benefits and risks of testing more thoroughly and in a more personal way (i.e., by imagining their

own reactions), they may have processed this information differently than those who received education only. However, contrary to expectations, neither the educational or counseling approach diminished intentions to have BRCA1 testing or to provide a blood sample. This finding suggests that other factors, such as patients' emotional states, may exert important influences on genetic testing decisions.

A recent study suggests that psychological distress may be an important determinant of patients' decisions to have genetic testing. In a study of women with a family history of breast-ovarian cancer, those who were more worried and distressed about their cancer risk were significantly more likely to participate in a breast-ovarian cancer risk counseling trial (18). Similarly, among relatives of ovarian-cancer patients, cancer worries and mood disturbance were positively related to intentions to have BRCA1 testing (19).

The association of psychological distress to actual use of BRCA1 testing was evaluated in the study of HBOC family members previously described (20). Prior to the offer of testing, measures of cancer-specific and general distress were administered. Overall, levels of distress were not clinically significant in this population. After controlling for demographic factors and risk status, cancer-specific distress was found to be significantly and positively related to BRCA1/2 testing. Individuals with moderate to high levels of cancer-related distress were about three times more likely to receive BRCA1 testing than individuals with low distress levels. This suggests that the presence of even a moderate degree of distress can motivate BRCA1/2 test use. The implication of this finding is that patients who present for BRCA1/2 testing may represent a more psychologically vulnerable subgroup of the high-risk population.

3.2. Psychosocial Outcomes of Testing

Until recently, our knowledge of the psychosocial consequences of genetic testing for breast-ovarian cancer susceptibility was based entirely on anecdotal reports. These reports warned of negative emotional reactions in carriers and noncarriers of BRCA1 mutations (2,21). However, in the past few years, several controlled investigations of the psychosocial impact of BRCA1 testing have been mounted, and interim data are available from a few of these studies.

The first of these studies focuses on the psychosocial effects of testing in a large HBOC kindred in Utah. The study protocol and measures were described (22). Croyle and colleagues (23) recently reported preliminary findings from the first 60 women who received BRCA1 mutation test results. Study participants were interviewed by telephone before being scheduled for their initial meeting with a genetic counselor. Test results were provided at a second meeting with a genetic counselor and a psychosocial counselor (a psychiatrist, psychologist, or marriage and family therapist). One to two weeks later, participants were interviewed again to assess their reactions to learning their mutation status.

The report by Croyle et al. (23) focused on the impact of BRCA1 testing on generalized anxiety and on distress related specifically to genetic testing. There was no significant change from baseline to follow-up in the level of general anxiety reported by carriers. Among noncarriers, there was a small but significant decline in general distress. On the measure of specific distress, however, one group showed significantly

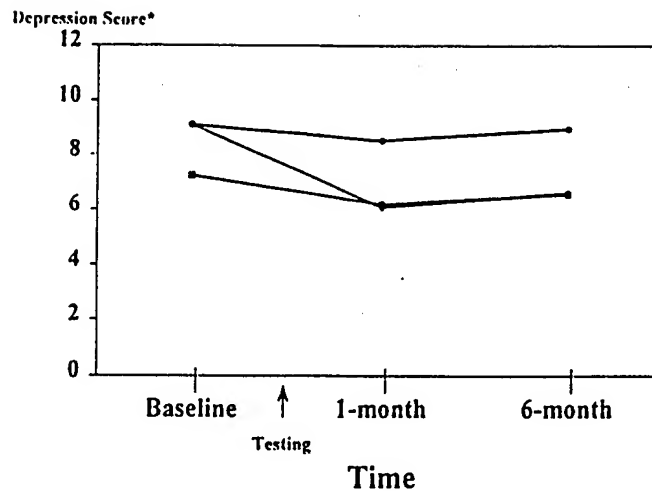


Fig. 2. Impact of BRCA1/2 testing on depressive symptoms in unaffected members of hereditary breast cancer families.

higher levels of disturbance when compared with the other participants. Even after controlling for baseline levels of general distress, women with no history of cancer or cancer-related prophylactic surgery reported higher levels of distress related to genetic testing. In contrast, mutation carriers who had already experienced cancer or prophylactic surgery showed no more distress than noncarriers.

Recently, we reported interim data from a prospective cohort study of members of several HBOC families in a registry maintained by Dr. Henry Lynch at Creighton University (4). Changes in depressive symptoms and functional impairment from baseline to 1-mo post-testing were reported for 46 carriers of BRCA1 mutations, 50 noncarriers, and 44 decliners of BRCA1 testing. At baseline and 1-mo follow-up, all three groups scored in the normal ranges on these measures. Noncarriers of BRCA1 mutations exhibited significant decreases in depressive symptoms and role impairment and marginally significant decreases in sexual impairment, compared to carriers and decliners. Carriers and decliners of testing did not exhibit changes in any of these distress outcomes. Unpublished 6-mo follow-up data from this cohort suggest that this pattern of responses is maintained over time (*see* Fig. 2).

Although these two initial reports do not provide evidence for significant or pervasive adverse psychological effects of BRCA1 testing, caution is warranted in generalizing these findings to other populations and settings. Participants in these studies were members of high-risk families in hereditary cancer registries, many of whom were involved in prior cancer genetics studies. These families had been included in the registries because of their unusually high cancer rates. As a consequence of witnessing cancer in many close family members, emotional responses of study participants may have been blunted. In fact, levels of distress were lower in these HBOC families than in population-based samples of women with a family history of cancer and cancer patients (20). In addition, most unaffected individuals in these high-risk families reported prior to testing that they expected to be mutation carriers. Thus, receiving a positive

test result may have confirmed what they believed to be true all along. In some cases, worrying about the possibility of being a mutation carrier may be no less distressing than having that belief confirmed. Individuals who have less significant family histories, and who do not expect to receive positive results, may be more vulnerable to adverse psychological sequelae of BRCA1 testing. It should also be noted that all individuals in these studies were Caucasian (all of the Utah subjects were Mormon) and most had a high school education. In addition, all testing was provided as part of research protocols with extensive education and counseling. Such counseling may be responsible for the observed psychological benefits in the Lerman et al. study (4).

3.3. Medical Outcomes of Testing

In order for BRCA1/2 testing to anticipated reductions in breast-ovarian cancer mortality, carriers must adopt recommendations for intensive and frequent surveillance (13). To date, there are no published data on the impact of BRCA1/2 testing on adoption of recommended surveillance practices. However, our preliminary data from the cohort of HBOC family members suggest that screening adherence is suboptimal. Only 39% of eligible carriers had recommended mammograms during the 6 mo following testing and only 6% had transvaginal ultrasound or CA-125.

Rather than participate in frequent cancer surveillance, some female carriers of BRCA1/2 mutations are opting for prophylactic mastectomy and/or prophylactic oophorectomy. It is important to note that, although this procedure may reduce cancer risk, there may be a 5–10% or higher residual risk of cancer after these organs are removed (24,25). In the cohort study previously described (4), among unaffected female BRCA1 carriers, 18% intended to obtain prophylactic mastectomies and 33% intended to obtain prophylactic oophorectomies. Additional research is needed to document rates of surgery and to evaluate the psychosocial effects and efficacy of these medical procedures.

Preliminary data suggest that reproductive plans and choices may also be altered by genetic testing for breast-ovarian cancer susceptibility. In a survey of 56 women ages 40 and younger who had a family history of breast-ovarian cancer, 22% reported that they would be less likely to have children if they tested positive for a BRCA1 mutation and 17% reported being uncertain as to whether they would complete a pregnancy under these circumstances (26). Moreover, 30% indicated that they would be interested in prenatal testing for BRCA1 and 30% would consider terminating a pregnancy if the fetus tested positive.

3.4. Economic Impact of Testing

In the current health care climate, the cost-effectiveness of genetic testing will be of paramount importance in the diffusion of this technology to clinical practice. To date, however, there has been limited attention to the cost-effectiveness of genetic testing for cancer susceptibility. In a recent analysis of the economic impact of genetic testing for hereditary nonpolyposis colon cancer, Brown and Kessler (27) estimated that the cost per year of life saved by testing is \$55,000. This estimate is in the range of the cost per year of life saved for other cancer prevention practices such as mammography screening (28). It should be noted, however, that any cost-effectiveness estimates for

genetic testing for breast-cancer susceptibility or for other cancers would be highly speculative. Such estimates are affected strongly by the prevalence and penetrance of known mutations, as well as the efficacy of surveillance and prevention strategies in mutation carriers and their adoption of these practices. However, a reduction in health-care costs could be expected for individuals in high-risk families found to be noncarriers, because they would not longer require such intensive surveillance or surgical procedures. As yet, very little data on these parameters are available, making it difficult to calculate precise estimates.

3.5. Social Impact of Testing

One of the most significant social risks of genetic testing for breast-cancer susceptibility is the potential for discrimination by insurance companies on the basis of one's genetic status. As previously mentioned, fear of insurance discrimination is a potent barrier to participation in genetic testing and persons who lack health insurance are significantly less likely to be tested (4). Although the experience with genetic testing for breast-cancer susceptibility is fairly recent, there are several documented cases of insurance discrimination on the basis of a variety of other genetic disorders (29). In a recent survey of over 300 individuals from families with genetic disorders, 25% of respondents reported that they have been refused health insurance on the basis of their genetic risk, 22% had been refused life insurance, and 13% had been discriminated against in the employment setting (30). A number of states in the U.S. have enacted legislation to address genetic discrimination (31) and recent federal legislation has enhanced the protection of genetic-testing participants. However, circumstances remain by which persons with increased genetic risk can be denied or refused insurance or be charged with excessively high premium rates.

4. CASE EXAMPLES TO ILLUSTRATE PSYCHOSOCIAL ISSUES

These vignettes are based on actual cases but have been modified to protect privacy.

Cases 1-3 are examples of informed consent/decision making issues about participation in testing.

4.1. Case #1

Annie is a 31-year-old married woman who was diagnosed with breast cancer at age 26. She underwent a unilateral mastectomy and chemotherapy and is now disease-free with a good long-term prognosis. Her paternal grandmother, who was diagnosed with ovarian cancer at age 60, is the only other case of cancer in the family. Her parents and her two older sisters are in good health (*see* pedigree in Fig. 3). The family is of Ashkenazi Jewish descent. Annie attended the genetic-counseling session with her husband, Jim. They were concerned mainly about cancer risks to future children based on Annie's medical and family history and were therefore very interested in pursuing genetic testing. Her oncologist had informed her that there was no medical contraindication for her to attempt pregnancy at this time. Jim's family history was noncontributory and he is not of Jewish descent.

During the genetic counseling session, they were informed that there have been three alterations in the BRCA1 and BRCA2 genes that occur with increased frequency in individuals of Jewish descent and that the chance of finding one of these alterations is

Case 1

Jewish

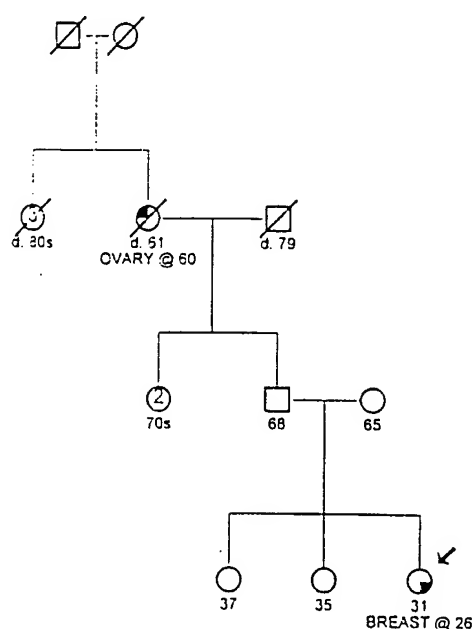


Fig. 3.

at least 20%, based primarily on Annie's young age at diagnosis. If an alteration was identified, then there would be a 50% chance of passing it down to future children. They were also counseled that a negative test result does not rule out the possibility of hereditary breast cancer, in which case future daughters would still face a somewhat increased risk of breast cancer based on empiric data. It was also explained that no one could guarantee the birth of a healthy child—that in fact, everyone has a few genes that do not work properly and it is not usually possible to know which genes are involved.

Much of the discussion focused on the couple's angst about the possibility of having a daughter who may be at risk for breast cancer. Jim also articulated his concern about Annie's prognosis. He wondered what would happen if she developed a recurrence and was not healthy enough to raise a child. He also was concerned about insurance issues. If Annie were to become ill again, he feared that losing or compromising their insurance because of a genetic test may deny them the resources they might need for state-of-the-art treatment such as bone-marrow transplant. Annie, however, was relatively unconcerned about developing cancer again. Nevertheless, these concerns about Annie provided the segue to discuss what genetic testing may be able to tell her, not about risk of metastatic disease as Jim had mentioned, but about her risk of developing breast cancer in her opposite breast and ovarian cancer, especially in the setting of a BRCA1 mutation. The conversation was then refocused to Annie, and secondarily to the issue of future children. Implications to her healthy parents and sisters were also considered. Annie was asked to imagine how she might cope with information that could affect her own health and the stability of relationships within her family. She imagined that her

Case 2

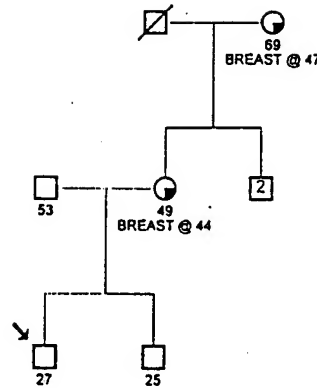


Fig. 4.

parent's feelings of guilt may be overwhelming, and as she considered her own future as a parent, she felt fearful and worried.

After several discussions with the genetic counselor over about a 12-mo period, Annie ultimately declined to get tested, and she is pregnant with her first child.

4.2. Case #2

Adam is a 27-year-old unmarried male whose mother and maternal grandmother recently learned that they have an alteration in the BRCA1 gene (*see* pedigree in Fig. 4). Adam's mother, a physician, reacted very positively upon learning her genetic testing results because she had always wanted to know why she and her mother developed early-onset breast cancer. She was very motivated to pursue early detection options for breast cancer (she had been treated with lumpectomy and radiation) and within 6 mo of learning her results, opted to have a prophylactic oophorectomy.

Adam presented for genetic counseling and testing, at his mother's strong urging, and said that he wanted to contribute a blood sample to "participate in research." He was somewhat indifferent about whether he wanted to receive results because he did not see that they would have any relevance to him. He did not perceive any "down sides" to testing and he specifically mentioned that he understood potential insurance risks but felt comfortable pursuing testing in a research setting where his results would be kept confidential.

Although it is recognized that many individuals choose to have genetic testing for a variety of reasons, including participating in research, he was not aware of at least two important issues that could impact him. One was that if he tested positive, current evidence suggests that his risk for prostate cancer and possibly colon cancer could be elevated. However, because these cancers do not appear to occur at early ages in male BRCA1 carriers, it is not clear that such information would affect his standard medical care in the future. In addition, if he were to test positive there would be a 50% chance that he could pass down the alteration to his children (boys and girls). He was also counseled about the fact that if he tested negative, his cancer risks

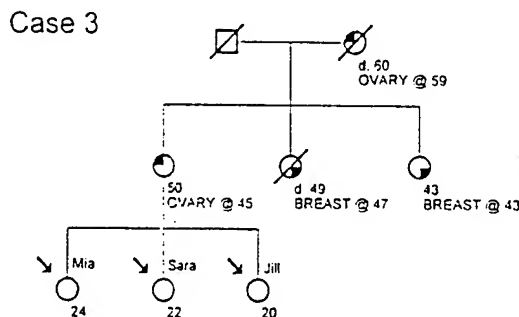


Fig. 5.

would be about the same as for other men in the general population and that he would know that the mutation could not be passed down to his children. He was also encouraged to consider the emotional implications should he test positive and to think through how his getting tested may affect decisions of his younger brother, how his mother may feel, and how he would communicate the information to a future spouse.

At the conclusion of the genetic counseling session, Adam decided to get tested, but articulated his main reason as concern for future children while also wanting to contribute to research. He was also very interested in obtaining his results. He later reported that while awaiting his results, he pursued discussions with his mother and brother about the potential impact on the family dynamics and was satisfied that these issues had been discussed openly and that he had a fuller appreciation for the potential impact of testing for himself and his family.

4.4. Case # 3

Three sisters, Jill, Sara, and Mia, ages 20, 22, and 24, attended a genetic counseling session together about 8 mo after learning that their mother had a BRCA1 alteration. Their mother, now age 50, is undergoing aggressive chemotherapy after a recent diagnosis of metastatic ovarian cancer. The family history is significant for two cases of early-onset breast cancer in their maternal aunts, and ovarian cancer in their maternal grandmother (*see* pedigree in Fig. 5). None of the sisters is married or has children. They are all in college or graduate school.

During the genetic counseling session, all the sisters verbalized their intentions to get tested and openly discussed their concerns about the implications of a positive result. For example, they were concerned about the lack of efficacy of cancer screening, particularly for ovarian cancer, and also for breast cancer in young women. They were not inclined to consider preventive surgery at this time. They wondered if a positive test result would affect decisions about oral contraceptive use, whether or when to have children, and how to raise the issue with future spouses. Although the sisters were participating in a free genetic counseling and testing research program with some measures in place to try to protect their privacy, they were also very worried about the potential effects of testing on their insurability. All of the sisters were covered at present under their parents' insurance and one sister had a part-time job with no benefits.

Another significant issue concerned the emotional implications of testing. The youngest sister, Jill, said that she hoped she would test positive because she felt that, as the youngest child, she had always gotten special attention, especially from her mother, and she felt best able to handle the information. Interestingly, the middle sister, Sara, remarked that she hoped they would all have the same result—that they should all learn that they have the alteration, or that they all do not have the alteration. She said that this way they could each understand what the others were experiencing—they would have a built-in support system, and no one would feel guilty or excluded. They commented that they have a very open relationship with their mother but were very concerned about her feeling guilty if any of them tested positive, and that she would become distracted from focusing on her own recovery. They were also aware of the large degree of reassurance they could obtain from negative test results. The oldest sister, Mia, was most certain about her decision to get tested. She had already been receiving more cancer screening than her younger sisters and also tried to reassure them that the potential benefits of testing outweighed the risks or limitations; even if the benefits were not immediate, she believed that the knowledge would be critical as they got older. She also comforted them by telling them that their mother has the emotional strength to support them in their decision about testing regardless of the outcome.

The genetic counseling session enabled the sisters to explore their feelings about testing outcomes and to consider the pros and cons of testing. Ultimately, they all suggested that the uncertainty associated with not knowing their genetic status would be more difficult than knowing one way or the other. Thus, Jill, Sara, and Mia all provided blood samples for testing, and were informed that the results would be available in about 1 mo, at which time they would be invited back for a disclosure visit.

When the results were available, Mia immediately scheduled her appointment. Before she learned of her results, Jill and Sara declined to schedule an appointment for follow-up. They cited concerns about insurance discrimination as their primary reason for declining at this time. They both said they wanted to wait to find out their results until they finished school and had jobs. Although they did not articulate concerns about feeling fearful or anxious about their results, it is quite likely that subsequent to these issues being raised and discussed openly during their initial session, they decided that this was perhaps information that they were not prepared to handle. Mia did test positive and expressed "relief" upon learning the result primarily owing to the reduction of uncertainty and interestingly, for solidifying a "bond" she had felt strongly to her mother—both emotionally and now genetically. She intended to share the information with her physicians in order to develop a plan for close surveillance and follow-up. In discussions with her over the next several weeks, Mia informed the genetic counselor that she communicated her test result to her sisters, and despite her own optimistic attitude, her sisters still chose not to receive their results.

Comment on cases 1–3: These cases illustrate that although it is important to address the issues presented by the patient, fully obtained informed consent means that the patient must be aware of the potential spectrum of issues that may arise, even if the information may be distressing. Helping patients to imagine how they would respond to this information, however, is a critical part of the genetic counseling process. Indi-

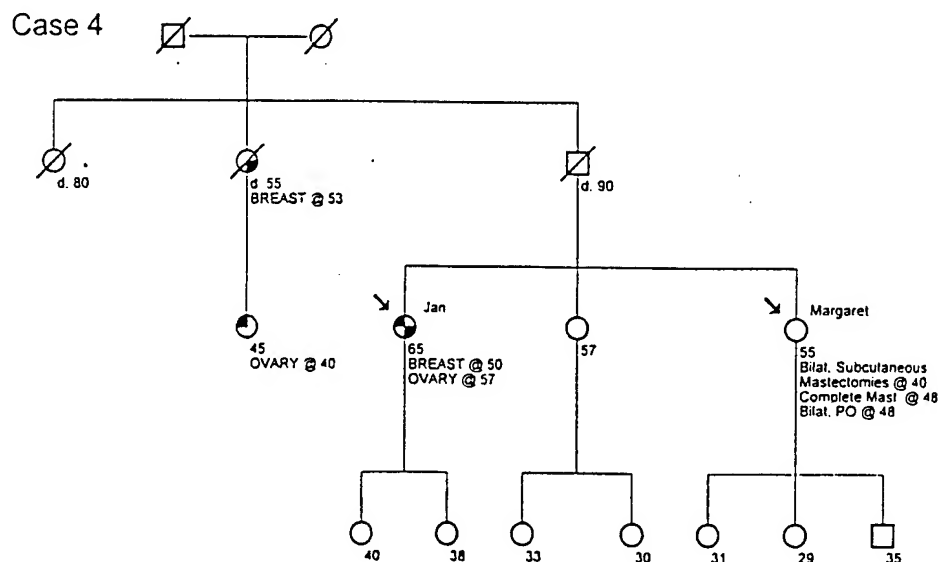


Fig. 6.

viduals considering testing do so for a variety of reasons, and their intentions and responses may change over time.

Cases 4 and 5 are examples of psychosocial and medical impact of genetic testing.

4.5. Case #4

Margaret is a 55-year-old woman who underwent bilateral prophylactic subcutaneous mastectomies at age 40—within a year after her oldest sister, Jan, was diagnosed with invasive breast cancer. About 8 yr later, Jan developed ovarian cancer. In the setting of Jan's diagnosis and the strong family history of breast and ovarian cancer as represented on the pedigree (see Fig. 6), Margaret was counseled by her physician to have her ovaries removed as a preventive measure, especially because she had recently become menopausal. At age 48, she underwent an oophorectomy and also had additional tissue removed from her breasts (in essence, she had "total mastectomies"). In 1996, Jan and Margaret participated in a genetic counseling session and were interested in obtaining BRCA1/2 gene testing. Jan was interested primarily to gain information for her children and sister. Margaret wanted to get tested to learn about risks for her children, especially her daughters.

Because Jan had a history of two primary cancers, genetic testing for BRCA1 alterations was offered first to her. A common mutation in the gene was identified and then testing was extended to Margaret, who had a 50% chance of having inherited the mutation. In a second counseling session, Margaret was asked to explore how she would feel in the setting of learning that she tested positive and also to consider how she would feel if she tested negative. She said that she fully expected to learn that she has the mutation identified in her sister. She based this reasoning on a combination of factors in her medical history (she had a history of benign breast biopsies and always had difficult menses) as well as her perception that she looked like her older sister and

that in general, "bad things seem to always happen" to her. Her decisions to undergo preventive surgery were based on these reasons as well as her anxiety about developing cancer. In the 7-15 yr since her surgeries, she remarked that she has enjoyed an exceptional and fulfilling quality of life. Her husband, family, friends, and coworkers have all provided support to her throughout this process. When asked to consider the implications of testing negative, she said that it would be the desirable, albeit unexpected, outcome because it would provide significant reassurance to her children and would eliminate the need to offer testing to them. The counseling session further reaffirmed that her decision to undergo surgery was an informed, reasonable choice, and for her was the best option. At the time, there was no way to help her to better quantify her risks for developing cancer other than that she could have a 50% chance of inheriting an altered gene that increased her cancer risk. She also realized that her satisfaction with this decision enabled her to be a productive, happy person in her personal and professional life.

During the next genetic counseling session, Margaret was informed that she did not carry the BRCA1 alteration identified in her family. She was delighted with this information because of the implications to her children. In several subsequent contacts with the genetic counselor, she has never expressed any regrets about her surgical decisions or choice to be tested.

4.6. Case #5

Two sisters, Rachel and Deborah, ages 40 and 45, tested positive for the BRCA2 alteration identified in their sister. As the pedigree illustrates (*see* Fig. 7), the family history of cancer other than their sister's diagnosis of breast cancer, is not very significant. Both Rachel and Deborah are accomplished, professional women. Rachel is married with three children; Deborah is single and has no children.

During the pre- and post-test counseling sessions, the sisters exhibited very different preferences for obtaining information. The elder sister wanted to get testing mostly owing to her curiosity, but was largely uninterested in hearing information about cancer risks associated with BRCA2 alterations and did not think that testing would affect her medical management or emotional well-being. She was already receiving breast exams every 3 mo along with annual mammograms. She also had regular gynecologic check-ups and because of the limited efficacy of ovarian cancer screening and the uncertainty about her ovarian-cancer risks, she did not think she would pursue ovarian screening or consider surgical options for risk reduction. Her sister, however, had a very different style of information seeking. She wanted to know many more details about the process of genetic testing, specific numerical risks associated with BRCA2 alterations and how they were derived, and data about screening and prevention options for breast and ovarian cancer. She was of the mind that, despite the uncertainties in cancer risks and efficacy of preventive measures, any heightened risk was too much to handle. She wanted to have prophylactic mastectomies and oophorectomy within the near future. She was also very concerned about her children, all of whom were too young to be tested. Whereas Rachel seemed very "panicked," Deborah seemed very complacent and did not appear to relate to Rachel's concerns.

During the counseling sessions, which both sisters attended together, their different perspectives were very evident. Deborah tried very hard to calm her sister whereas

Case 5

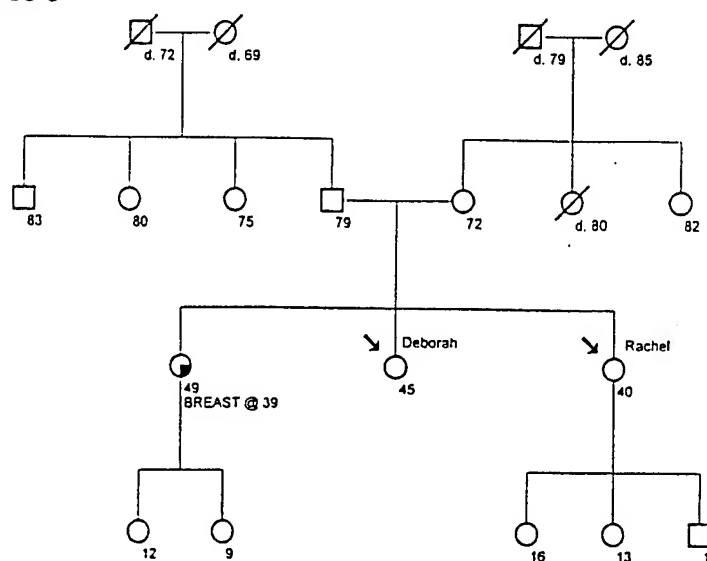


Fig. 7.

Rachel perceived Deborah as being apathetic and uninterested in the implications of their results. The ensuing discussion raised issues such as the idea that each person responds differently to this information, that there is no right or wrong way to feel, and that medical decision-making is a very personal matter. They were counseled to think carefully about the information, not to make any hurried decisions, and to realize that their decisions and feelings may vary over time. For example, one could opt for close screening now but consider surgical options in the future. One alternative that both sisters decided to investigate was a new chemopreventive agent for women at high risk for breast cancer. In so doing, Rachel was allowing herself to consider an option other than preventive surgery and Deborah was acknowledging that she was concerned about her cancer risks and would probably feel better if she knew she had carefully considered all alternatives for medical management.

In the 6 mo since their disclosure visit, both are still considering the chemoprevention trial, and Rachel is undecided about prophylactic surgery. She, however, continues to be very distressed and anxious, and was referred for follow-up psychological counseling.

Comment on cases 4-5: These cases illustrate that choices about medical management are highly individualized, as are the overall responses to learning genetic testing results. Psychological distress may make it difficult for patients to cope successfully with new information about their cancer risks, and may also hamper their ability to prioritize courses of action with respect to medical decisions, communication with family members, and dealing with their own emotions. The genetic counseling process can often help to prepare patients for these tasks by providing them with information and supportive counseling.

5. CONCLUSION

Discoveries of breast cancer susceptibility genes raise hopes concerning the public health benefit of genetic testing. However, before clinical counseling and testing programs are established on a widespread basis, effective and ethical means of communicating genetic risk information must be identified. Genetic counseling and testing protocols must be informed by empiric research that examines the psychosocial and clinical impact of testing programs on participants and their family members. In addition, further research is needed to elucidate individual differences in the psychosocial and health-behavioral outcomes of genetic testing so that counseling strategies can be matched to individual patient needs. Consensus guidelines for surveillance and prevention should also be refined further as empiric data become available. At the same time, methods for enhancing patient adherence to recommended surveillance practices should be developed and validated. These issues will be best addressed if genetic testing for breast cancer susceptibility is conducted within the context of research that carefully assesses the immediate and long-term impact of participation in genetic counseling and testing programs.

ACKNOWLEDGMENTS

The authors would like to thank Henry Lynch, Steven Narod, and Stephen Lemon for their contributions to the work reported in this chapter, and Susan Marx for her assistance with manuscript preparation.

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Breast Cancer

*Molecular Genetics, Pathogenesis,
and Therapeutics*

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Humana Press  Totowa, New Jersey

Acknowledgments

Robert Dickson (Lombardi Cancer Research Center, Georgetown University) and Tony Brown (Cornell University and the Strang Center Research Laboratory, Rockefeller University) provided invaluable suggestions regarding the content of this book.

This book would not have been completed without the dedication and competence of Colleen Campbell.

To all the authors of individual chapters, I am profoundly grateful, as I am to reviewers who provided valuable and incisive criticism and suggestions.

Finally, to my husband, Michael Lovett, I am constantly appreciative of his tireless support, patience, and a sense of humor that never wanes.

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Totowa, New Jersey 07512

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ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Cover design by Patricia F. Cleary.

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data

Breast cancer: molecular genetics, pathogenesis, and therapeutics / edited by Anne M. Bowcock.
p. cm.—(Contemporary cancer research)

Includes index.

ISBN 0-89603-560-3 (alk. paper)

1. Breast—cancer. 2. Breast—Cancer—Genetic aspects. I. Bowcock, Anne M. II. Series.

[DNLM: 1. Breast Neoplasms—genetics. WP 870 B8211342 1998]

RC280.B8B66555 1998

616.99'449—dc21

DNLM/DLC

for Library of Congress

98-21525
CIP

PROJECT 1: APPENDIX 2 SELECTED ABSTRACTS

DeMarco TA, Peshkin BN, Brogan BM. Genetic counseling for breast and ovarian cancer susceptibility: closing the gap. Revised manuscript in preparation for the Journal of Genetic Counseling.

Genetic counseling for cancer predisposition involves a comprehensive process of risk assessment and communication, in addition to a discussion of medical and psychosocial issues. When testing is an option, the complexity of these concerns may be further magnified. In this paper, we present vignettes based on four participants counseled as part of a clinical research program. Within this program, certain patient populations can be delineated, each with unique sets of issues. These groups include newly diagnosed breast cancer patients, women with recurrent or metastatic disease, men with breast cancer, and young unaffected women at-risk for a familial mutation. Through the use of detailed vignettes, multifaceted issues that arise in cancer genetic counseling are highlighted, as well as concepts that can be applied globally to counseling individuals regarding adult onset hereditary conditions.

Isaacs C, Peshkin BN, Schwartz M, DeMarco TA, Main D, Lerman C. Breast and ovarian cancer screening practices in healthy women with a strong family history of breast or ovarian cancer. Manuscript in preparation.

Purpose: To assess baseline breast and ovarian cancer screening behaviors and related determinants in a clinic-based group of women with a strong family history of breast or ovarian cancer.

Patients and Methods: Participants were 216 healthy females from hereditary breast cancer families. As part of a free genetic counseling and testing research program, they completed a baseline telephone interview between 1995-1999 which assessed demographics; family and medical history; breast and ovarian cancer screening practices; and psychological variables.

Results: Overall, 86% of participants had a clinical breast exam in the previous year. Fifty percent of women ages 30-39, 83% of those age 40-49, 69% of those 50-64, and 53% of those over the age of 65 had a mammogram in the prior year. Twenty percent of participants had had at least one CA-125 performed and 31% had ever obtained a screening ultrasound. Having at least 1 relative with ovarian cancer was very strongly associated with ovarian cancer screening [OR=12.3, 95% CI = 4.6-33 for CA-125; OR = 4.9, 95% CI = 2.4,10.1 for ultrasound]. Perceived and objective cancer risks were also independent predictors of uptake for CA-125 and ultrasound. No association between cancer worries/distress and either breast or ovarian cancer screening was found.

Conclusion: Breast and ovarian screening uptake in healthy women from hereditary breast cancer families is suboptimal, even for women over age 50, for whom annual mammography is clearly indicated. Health care providers and patients need to be better informed about screening recommendations for high risk women, and the fact that women with a strong family history of breast cancer may also be at-risk for ovarian cancer.

Peshkin BN, DeMarco TA, Brogan BM, Lerman C, Isaacs C. BRCA1/2 testing: complex themes in result interpretation. Revised manuscript under review at Journal of Clinical Oncology.

[Excerpted from the introduction.] Several years after BRCA1 and BRCA2 were cloned, we have a better understanding of the pertinent scientific and psychosocial issues, but are still faced with many of the complexities and uncertainties we encountered earlier. We know that patient decision-making about genetic testing and how to utilize such information is not a simple process. Even when a positive result (i.e., a deleterious mutation) is identified, the associated cancer risks cannot be precisely quantified and the efficacy of management options is still very uncertain. And when a negative result is obtained, it could be good news fraught with survivor guilt (in the case of a true negative for a familial mutation), or as this paper focuses on, a negative result could be completely ambiguous and raise more questions than it answers. Addressing this issue is especially important because a significant proportion of high-risk families do not harbor deleterious mutations in BRCA1 or BRCA2. For example, studies have demonstrated that 16-66% of high-risk families do not carry detectable mutations in these genes.

Thus, even though interpretation of BRCA1/2 results is relatively straightforward in many circumstances, complex cases are not infrequently encountered in the clinical setting. In such instances, alternative explanations for test results need to be considered, additional family members may need to be tested, or participation in research studies may be indicated. The focus of this paper is to illustrate some of these complex themes in genetic counseling. We present five vignettes based on actual cases drawn from our clinical research program, through which high-risk individuals receive genetic counseling and testing at no cost. These vignettes and pedigrees have been modified to protect patient and family confidentiality. The commentaries following each case highlight concepts that can be applied globally to the process of cancer risk counseling.

Schwartz MD, et al (authorship to be determined). The impact of BRCA1/BRCA2 mutation testing on psychological distress in a clinic-based sample. Manuscript in preparation for Journal of the National Cancer Institute.

Despite the increasingly widespread availability of clinic-based genetic testing for the BRCA1 and BRCA2 breast cancer susceptibility genes, little is known about psychological impact of such testing. The objective of this study was to examine the long-term psychological impact of receiving BRCA1/BRCA test results within a clinic-based testing program. Participants were 289 women with familial breast cancer who underwent genetic counseling and testing for alterations in the BRCA1 and BRCA2 genes. At baseline (prior to genetic testing) and at six-months following the disclosure of BRCA1/2 mutation status, we measured perceived risk for breast and ovarian cancer, cancer-specific distress, and general distress. We examined the impact of mutation test result on each of these outcomes. Analyses were conducted separately for probands (who had been previously diagnosed with breast and/or ovarian cancer) and their unaffected relatives. Among affected probands (who could receive either a positive BRCA1/2 test result or an uninformative test result), we found that test result was unrelated to any of our outcomes. Among unaffected relatives (who could receive either positive or definitive negative test results), we found that test result was associated with each of our outcomes. Specifically, using generalized estimating equations, we found that relatives who received negative test results

exhibited significant reductions in perceived risk, cancer-specific, and general distress compared to participants who received positive test results. Importantly, those relatives who received positive test results did not exhibit increases in distress or perceived risk. Rather, their distress levels did not change from baseline to follow-up. These results suggest that clinic-based BRCA1/2 testing can lead to psychological benefits for individuals who receive negative test results. Those who receive positive or uninformative test results do not exhibit increased psychological distress or perceived risk.

Tercyak KP, Lerman C, Peshkin BN, Hughes C, Main D, Isaacs C, Schwartz MD. Effects of coping style and test result on anxiety among women participation in genetic counseling and testing for breast/ovarian cancer risk. Health Psychology (in press)

Using the monitoring process model (MPM), the authors examined the immediate effects of coping style and test result on the psychological distress of women at increased risk for breast/ovarian cancer. Cases selected for analysis were 107 probands and relatives of positive probands participating in genetic counseling and testing for heritable cancer risk. Specifically, we explored the relationships among coping style (high and low monitoring), test result (BRCA1/2 mutation carrier and noncarrier status), and psychological distress (state anxiety). Consistent with the MPM, higher monitoring was associated with greater psychological distress while anticipating genetic test results. After test results were disclosed, greater distress was associated with testing positive for a mutation. The implications of the findings for breast/ovarian cancer patients are discussed.

PROJECT 3: APPENDIX 1
BAIDAS REPRINT

Phase II Evaluation of Thalidomide in Patients With Metastatic Breast Cancer

By Said M. Baidas, Eric P. Winer, Gini F. Fleming, Lyndsay Harris, James M. Pluda, Jeanette G. Crawford, Hideko Yamauchi, Claudine Isaacs, John Hanfelt, Mariella Tefft, David Flockhart, Michael D. Johnson, Michael J. Hawkins, Marc E. Lippman, and Daniel F. Hayes

Purpose: To determine the efficacy, safety, pharmacokinetics, and effect on serum angiogenic growth factors of two dose levels of thalidomide in patients with metastatic breast cancer.

Patients and Methods: Twenty-eight patients with progressive metastatic breast cancer were randomized to receive either daily 200 mg of thalidomide or 800 mg to be escalated to 1,200 mg. Fourteen heavily pretreated patients were assigned to each dose level. Each cycle consisted of 8 weeks of treatment. Pharmacokinetics and growth factor serum levels were evaluated.

Results: No patient had a true partial or complete response. On the 800-mg arm, 13 patients had progressive disease at or before 8 weeks of treatment and one refused to continue treatment. The dose was reduced because of somnolence to 600 mg for five patients and to 400 mg for two and was increased for one to 1,000 mg and for four to 1,200 mg. On the 200-mg arm, 12 patients had progressive disease at or before 8

weeks and two had stable disease at 8 weeks, of whom one was removed from study at week 11 because of grade 3 neuropathy and the other had progressive disease at week 16. Dose-limiting toxicities included somnolence and neuropathy. Adverse events that did not require dose or schedule modifications included constipation, fatigue, dry mouth, dizziness, nausea, anorexia, arrhythmia, headaches, skin rash, hypotension, and neutropenia. Evaluation of circulating angiogenic factors and pharmacokinetic studies failed to provide insight into the reason for the lack of efficacy.

Conclusion: Single-agent thalidomide has little or no activity in patients with heavily pretreated breast cancer. Further studies that include different patient populations and/or combinations with other agents might be performed at the lower dose levels.

J Clin Oncol 18:2710-2717. © 2000 by American Society of Clinical Oncology.

THALIDOMIDE, A derivative of glutamic acid, was introduced in Europe in 1954 as a sedative/hypnotic agent and was used to ameliorate nausea in pregnancy.¹ Peripheral neuritis attributable to thalidomide was reported in patients after long-term use.^{2,3} Other reported side effects included somnolence, nausea, dry mouth and skin, constipation, urticaria, headaches, irregularities in menstrual cycles, hypothyroidism, and edema of lower extremities.⁴⁻⁸ Although thalidomide was well tolerated, with no apparent severe toxicities or addictive properties, a large increase in the incidence of limb malformations (amelia and phocomelia)

lia) in newborn children was observed as a result of thalidomide use during pregnancy.^{9,10} Thalidomide was withdrawn from the market in Europe by the end of 1961, and it was never marketed in the United States.

Despite these toxicities, clinical trials of thalidomide for other indications were performed. In 1998, thalidomide was approved by the Food and Drug Administration for the treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum. Thalidomide also has activity in the treatment of cutaneous lupus erythematosus, recurrent erythema multiforme, recurrent aphthous ulcers (especially in patients with AIDS), and graft-versus-host disease after transplantation.^{5,11-15} Although the exact mechanism of this immune-modulating activity is unclear, it might be secondary to inhibition of lymphocyte proliferation or to modulation of integrin receptors on human WBCs.^{16,17} Thalidomide also inhibits tissue necrosis factor alpha (TNF- α) production by stimulated human monocytes and lymphocytes, possibly by enhancing mRNA degradation.¹⁸⁻²⁰

Soon after thalidomide was withdrawn from the market in 1961, reports of a disease response or stabilization in a patient with sarcoma treated with this agent prompted clinical studies in other patients with cancer.⁶ Thalidomide was administered to 21 patients with 14 types of cancer at doses ranging from 600 to 1,400 mg/d. No tumor regres-

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Submitted December 1, 1999; accepted March 10, 2000.

Supported by Department of Defense Cancer Center grant no. DAMD17-96-C-6069 and by Fashion Footwear Association of New York. "Shoes on Sale."

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0732-183X/00/1814-2710

sions were noted, but subjective palliation was reported in seven patients. In two patients (with multiple myeloma and fibrosarcoma), the rapid progression of the disease seemed to be slowed.⁶ In another study, 71 patients with a wide spectrum of cancers were treated with thalidomide at variable doses ranging from 300 to 2,000 mg/d. In this trial, only one objective response was observed in a patient with renal cell cancer whose pulmonary lesion disappeared after treatment.⁷ However, in more recent studies, responses to thalidomide in patients with multiple myeloma and brain tumors have been reported.^{21,22}

New blood vessel formation is an essential step in the establishment and growth of malignancies. Angiogenesis has acquired importance as an independent prognostic indicator in solid tumors.²³⁻²⁵ Importantly, tumor angiogenesis in invasive breast cancer correlates with the presence of local and distant metastasis.²⁶⁻²⁸ In addition to its immunomodulatory activities, thalidomide also inhibits angiogenesis. Indeed, one of the proposed mechanisms for the teratogenic activity of thalidomide is axial limb artery degeneration.²⁹⁻³¹ For example, deformed tails from puppies treated with thalidomide seem to have been deprived of blood supply.³⁰ Oral thalidomide inhibits angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in the rabbit corneal micropocket assay.^{32,33} This effect results from a direct inhibition of angiogenesis rather than from thalidomide immune-modulatory activity.

Taken together, the direct antiangiogenic activity of thalidomide, its availability in a well-tolerated oral form, the availability of safe and effective birth control methods, and the apparent importance of angiogenesis in development, growth, and metastasis of malignant tumors prompted the initiation of thalidomide clinical trials in the treatment of cancer. We report the results of the first single-disease, prospective, phase II study of thalidomide in patients with metastatic breast cancer.

PATIENTS AND METHODS

Patient Selection

This prospective phase II clinical trial was conducted after obtaining protocol approval from the institutional review boards of the participating institutions. Eligible patients must have been 18 years or older and have had histologically confirmed metastatic breast cancer with documented progressive disease. Patients must have had assessable or bidimensionally measurable disease in at least one site. Patients with assessable bone-only disease were required to have a lytic lesion that had not been radiated previously. Ascites and pleural effusions were not considered as measurable or assessable disease. Patients may have had no more than three prior chemotherapy regimens. One adjuvant chemotherapy was permitted in addition to two regimens for metastatic disease. If no adjuvant chemotherapy was given, then as many as three

chemotherapy regimens for metastatic disease were allowed. There were no limitations to previous hormonal or biologic therapies. Patients had to be ambulatory with Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients had to have clinically adequate organ function as follows: WBC count $\geq 3,000$ cells/ μ L; hemoglobin level ≥ 8 g/dL; platelet count $\geq 75,000$ cells/ μ L; prothrombin time and partial thromboplastin time less than 1.25 times the upper limit of normal; bilirubin, AST, ALT, and alkaline phosphatase levels no greater than 1.5 times the upper limit of normal; magnesium level ≥ 1.8 mg/dL; and serum creatinine level no greater than 1.5 times the upper limit of normal. Patients must have recovered from the reversible side effects of any prior therapy. Negative serum pregnancy testing was required within 48 hours of the first dose and monthly thereafter for all women with childbearing potential.

Exclusion criteria included the following: recent major surgery within 21 days from starting treatment on protocol; frequent vomiting and severe anorexia; chemotherapy, radiotherapy, or hormonal therapy within 4 weeks of study entry; presence of brain metastasis, carcinomatous meningitis, or cardiomyopathy; and grade 2 or greater peripheral neuropathy. Chemotherapy, radiation therapy, hormonal therapy, immune therapy, and investigational drug therapy were prohibited during treatment on protocol.

Study Design

This investigation was a multicenter (Georgetown University, University of Chicago, Dana-Farber Cancer Institute, and Duke University), open-label, randomized phase II study of thalidomide in patients with metastatic breast cancer. The primary objective was to assess whether thalidomide has activity in this setting and to detect any suggestion of any differences in activity between the high- and low-dose arms of thalidomide by evaluating percentage of patients who remained progression free at 2 months of therapy and by evaluating time to progression for patients who continued on treatment beyond the first 2 months. Safety profiles of the high- and low-dose arms of thalidomide were also obtained. The secondary objectives were to determine the objective response rate (complete and partial), to analyze effects of thalidomide on serum expression of bFGF, TNF- α , VEGF, matrix metalloproteinase activity (MMP-2 and MMP-9), and to study thalidomide pharmacokinetics.

Patients were stratified according to the number of previous chemotherapy treatments, zero or one versus two or three, and then randomized to one of two thalidomide doses: low dose (200 mg/d) or high dose (800 mg/d). Escalation by 200 mg every 2 weeks at the 800-mg/d arm was permitted in patients with no toxicity to a maximum of 1,200 mg/d. Thalidomide was given at 9 PM. Patients were asked to start taking laxatives along with thalidomide and to taper off any sedative or hypnotics they were taking. Patients received thalidomide as long as there was no evidence of tumor progression and as long as there was no dose-limiting toxicity. In the absence of new symptoms, the first tumor assessment was performed at week 8 of therapy. Patients with progressive disease were taken off study. All others continued therapy if toxicity was acceptable. Tumor assessment thereafter was performed every 2 months. Complete response was considered as the disappearance of all clinical and laboratory signs and symptoms of the disease for at least 4 weeks. Partial response was defined as a minimum reduction of at least 50% in the sum of the products of the longest perpendicular diameters of all indicator lesions. Progressive disease was defined as the appearance of new lesions or an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions. Stable disease was considered failure of the patient to qualify for complete or partial response or progressive

disease at 2 months or more. Patients were observed and evaluated for toxicity by history and physical examination every 2 weeks for the first 2 months and monthly thereafter.

Thalidomide was withheld for grade 2 neurotoxicities, except drowsiness and somnolence, until resolution to less than or equal to grade 1 and then restarted at a 25% dose reduction of the original dose. For recurrent grade 2 neurotoxicity, either thalidomide was restarted at 50% of the original dose after toxicity resolution to less than or equal to grade 1 or the patient was removed from the study. If the patient developed intolerable drowsiness or somnolence at the starting dose of 200 mg/d, the dose was reduced to 100 mg/d. If the patient developed intolerable drowsiness and somnolence at the starting dose of 800 mg/d, the dose was reduced to 600 mg/d, and if she continued to be drowsy, to 400 mg/d, then to 200 mg/d, and finally to 100 mg/d. If the patient could not tolerate the 100 mg/d, then she was removed from the study. Patients were taken off study for grade 4 toxicities except hematologic toxicities. For hematologic toxicities, only grade 4 toxicity was considered dose limiting. For patients with grade 4 hematologic toxicities, the drug was withheld until resolution to grade 1 and then restarted at 75% of the original dose. Patients with recurrent grade 4 hematologic toxicities were removed from the study. For other dose-limiting toxicities, the drug was withheld until toxicity resolved to grade 1 and then restarted at 75% of the original dose. Re-evaluation occurred at weekly intervals. If it was not possible to resume therapy after 3 weeks of delay because of persistent treatment-related toxicities, the patient was removed from the study. For recurrent toxicities, the drug was withheld until toxicity resolved to grade 1 and then restarted at 50% of the original dose. For recurrent toxicities while at a 50% dose reduction, patients were removed from the study.

Pharmacokinetics and Correlative Studies

The first dose of thalidomide was given at 9:00 AM on day 1. Subsequent doses were given at 9 PM. Plasma samples were obtained for pharmacokinetics immediately before the first dose on day 1 and then ½, 1, 1 ½, 2, 3, 4, 5, 6, and 7 hours after ingestion and at 9 AM and 1 PM on day 2. Pharmacokinetic specimens were collected every 2 weeks for the first 2 months and monthly thereafter. Thalidomide was assayed in plasma by modification of the method of Eriksson et al.³⁴ Plasma samples for assay of thalidomide were collected and diluted immediately into Sorenson's buffer (25 mmol/L disodium citrate pH 1.5) and then stored at -70°C before assay. Samples were thawed and kept on ice before further processing. Two milliliters of each plasma sample were placed in polytetrafluoroethylene-lined, screw-cap centrifuge tubes, and 50 µL of a 100-µg/mL solution of phenacetin was added. Samples were then subjected to vigorous vortex, and 5 mL of diethyl ether was added to each sample and the tubes capped before being shaken in an Eberbach mechanical shaker (Eberbach, Ann Arbor, MI) for 5 minutes. They were then centrifuged at 4,000 rpm in a Beckman J-6M centrifuge (Beckman, Fullerton, CA) with a JS 4.0 rotor for 5 minutes, and the ether layer was aspirated and placed in 12 × 75 mL culture tubes. The ether was evaporated by Speed-Vac (Savant Speed-Vac, Farmingdale, NY), and samples were reconstituted with 100 µL of the mobile phase below. Thalidomide was measured by high-performance liquid chromatography using an ALLTECH Spherisorb ODS-2 (250 × 4.6 mm) column (ALLTECH, Deerfield, IL), with a Waters Nova-Pak C₁₈ guard column (Waters, Milford, MA) both equilibrated in a mobile phase of water and acetonitrile (65/35 vol/vol). Using a pump speed of 1 mL/min, thalidomide was detected at 300 nm at a retention time of approximately 5.4 minutes, whereas the internal standard phenacetin was detected at approximately 6.75 minutes. By use of this method, the limit of quantification for thalidomide was

found to be 0.1 µg/mL and the inter- and intraday coefficients of variation at this concentration were less than 14.5% and less than 9.7%, respectively.

Serum specimens for angiogenic factors were obtained on day 1 immediately before the first dose of thalidomide, every 2 weeks during the first 2 months, and then monthly. Circulating levels of bFGF, VEGF, and TNF-α were determined using quantitative sandwich enzyme immunoassay kits according to the manufacturer's instructions (Quantikine, R & D Systems, Minneapolis, MN). Cutoffs to distinguish elevated levels were determined as the mean + 1 SD (84th percentile) of a normal population. These cutoff values were 9.0 pg/mL for bFGF, 429 pg/mL for VEGF, and 3.9 pg/mL for TNF-α.

Levels of plasma MMP-2 and MMP-9 were measured using zymograms, as described previously.³⁵ Briefly, patient plasma samples were diluted in 1 × zymogram loading buffer and run without boiling on 10% SDS Page gels (Sigma, St Louis, MO) that contained 0.1% gelatin. Conditioned media, treated with P-amino-phenyl-mercuric-acetate, from Hs578t and MDA-MB-231 cells were run on each gel to provide standards for the latent and active forms of MMP-2 and MMP-9. The gels were subsequently washed twice for 30 minutes in Tris-buffered saline that contained 2% Triton X-100 and then incubated overnight at 37°C in 50 mmol/L Tris pH 7, 5 mmol/L calcium chloride, and 1% Triton X-100 (Sigma) to allow gelatin degradation. Areas of digestion were then visualized by staining with Coomassie blue R250 (Sigma) in 10% acetic acid/20% methanol, followed by de-staining in 10% acetic acid/20% methanol. The gels were then dried, and the areas of clearing caused by the action of MMP-2 and MMP-9 were measured by image analysis of the appropriate portion of the gels.

Thalidomide Supply

Thalidomide was supplied by the National Cancer Institute-Cancer Therapy Evaluation Program. Thalidomide was provided as 100-mg tablets.

Statistical Methods

A two-stage sample design was used to evaluate whether thalidomide had any activity in patients with progressive metastatic breast cancer who had previously received zero to three chemotherapy regimens. Thalidomide was to be considered active in this patient population if at least 20% of the patients remained progression-free after 2 months on either arm of the study. In the first stage, 14 patients were entered onto each of the two arms by random assignment. The randomization was stratified by the number of prior chemotherapy regimens received (zero or one v two or three). If all of the first 14 patients on each arm progressed within 2 months on study, then the arm was to be terminated and it would be concluded that there was 95% confidence that thalidomide at the administered dose level was not active.³⁶ Alternatively, if at least one of the first 14 patients had stable disease or an objective response after 2 months on study, then the trial was to proceed to the second stage.

Serial circulating growth factor levels were determined for all but two patients. To evaluate whether relative changes in serial factor levels were significant, patients whose angiogenic factor levels never exceeded the cutoffs distinguished by 1 SD above the mean of a normal population were considered noninformative. Noninformative patients were excluded from these analyses because normal biologic changes may cause small absolute changes in marker levels within normal level range, and these small absolute changes may falsely represent large relative changes in serial levels. Furthermore, the standard curves for these assays are increasingly flatter toward the normal ranges. There-

Table 1. Patient Characteristics

Characteristic	Thalidomide Dose Level			
	200 mg (n = 14)		800 mg (n = 14)	
	No. of Patients	%	No. of Patients	%
Age				
30-40 years	1	7	3	21
41-50 years	7	50	2	14
51-60 years	5	36	4	29
61-70 years	0	0	4	29
71-85 years	1	7	1	7
Prior chemotherapy regimens				
0 or 1	2	14	2	14
2 or 3	12	86	12	86
High-dose chemotherapy with PBSC support	3	21	2	14
No. of hormonal therapy courses				
0 or 1	7	50	5	36
2-4	7	50	9	64
Site of disease				
Bone only	1	7	0	0
Lymph node only	3	21	1	7
Liver only	1	7	1	7
Chest wall only	1	7	0	0
2-4 sites	8	57	12	86

Abbreviation: PBSC, peripheral-blood stem-cell.

fore, small changes in the assay readout (for example, absorbance) are reflected as large relative changes in marker levels in this part of the curve. For example, if a normal cutoff is 2 U/mL, then 84% of the normal population are expected to have levels less than 2 U/mL. For both technical reasons (flat standard curve in this range) and biologic reasons (normal variation of 1 or 2 U/mL), a 50% change (from 1 to 2 U/mL) would not be considered likely to be a result of a therapeutic intervention. In contrast, the standard curves become quite linear and steep in ranges above the normal cutoff. Furthermore, normal biologic changes continue to account for serial changes of only 1 or 2 U/mL. Therefore, a 50% change (from 10 to 20 U/mL) is most likely to result from therapeutic intervention and not from biologic or technical causes. For these reasons, a relative change from baseline to a subsequent sample level was only considered informative if one, the other, or both sample levels exceeded the normal cutoff. To normalize the data, the natural logarithm of each marker level measurement at baseline and at time of removal from study (because of progression or toxicity) was taken. The log of the baseline level was subtracted from the log of the value at time of removal from study for each patient. Combining data from both dose levels, a paired *t* test was performed for each growth factor to test whether the mean difference from baseline to time of removal from study was statistically significant.

RESULTS

Patients

Twenty-eight patients were accrued at the four centers between 1996 and 1998 (Table 1). Fourteen patients were accrued to each of the two dose levels. Patients' ages varied from 30 to 85 years, with the largest number of patients between 41 and 60 years old (18 patients). Two patients on

Table 2. Reasons for Leaving Study

Dose Level	Progressive Disease (no. of patients/ total patients)	Patient Choice (no. of patients/ total patients)	Toxicity (no. of patients/ total patients)
200 mg	13/14	0/14	1/14
800 mg	13/14	1/14	0/14

each arm had had zero or one chemotherapy regimens before enrollment, and twelve had had two or three prior chemotherapy regimens. Three patients on the low-dose arm and two on the high-dose arm had received high-dose chemotherapy with peripheral stem-cell support before enrollment onto the protocol. Patients on the two treatment arms were comparable with respect to age and the number of chemotherapy regimens.

Dose Modifications

One patient at the 200-mg dose required dose reduction because of grade 3 peripheral neuropathy. At the 800-mg dose, five patients had to reduce doses to 600 mg and two patients to 400 mg, all because of neurotoxicity (somnolence). Two patients continued at the 800-mg dose with no changes. One patient's dose was increased to 1,000 mg, and four had their dose escalated to 1,200 mg.

Efficacy

No patient achieved a partial or complete response. Two patients at the 200-mg dose had stable disease at 8 weeks. The first patient had a 43% reduction in size of hilar and mediastinal lymphadenopathy (site of measurable disease) at 8 weeks. However, at the staging at 16 weeks, she had progressive disease and was removed from the study. This patient had previously received adjuvant chemotherapy with cyclophosphamide and doxorubicin and, later, paclitaxel and then vinorelbine for metastatic disease. The second patient had relatively indolent chest-wall disease that was slowly progressing on no treatment over the 20 months preceding thalidomide. At the staging at 8 weeks, she had stable disease, but she was removed from the study at week 11 because of grade 3 peripheral neuropathy.

As of August 26, 1998, all patients had been removed from the study, 26 because of progressive disease and two because of patient choice and/or unacceptable toxicity (Table 2). Of the two patients who did not progress, one was on the 200-mg arm and was removed from study at week 11 because of grade 3 peripheral neuropathy. The second patient was on the 800-mg arm and refused to continue treatment beyond week 4 because of drug-related somnolence. This patient refused dose reduction.

Table 3. Duration of Treatment

Dose Level	Duration in Weeks (no. of patients)					
	2	4	6	8	11	16
200 mg	1	1	0	10	1	1
800 mg	0	2	4	8	0	0
Total	1	3	4	18	1	1

At the 200-mg level, one patient was taken off study at 2 weeks and a second patient at 4 weeks after starting treatment because of rapidly progressive disease. Ten patients were taken off at 8 weeks because of progressive disease detected by routine restaging. Two patients went beyond the first 8 weeks of staging. The first patient was removed from study at 11 weeks and the second at 16 weeks (Table 3).

At the 800-mg level, two patients were removed from the study at 4 weeks, one because of progressive disease and the second, who refused to continue treatment, because of somnolence. Four patients were taken off study at 6 weeks and eight patients at 8 weeks, all because of progressive disease. None of the patients at the 800-mg level continued beyond the first 8 weeks of treatment (Table 3).

Adverse Events

Only one patient was removed from the study because of grade 3 neurotoxicity (peripheral neuropathy). This patient was on the 200-mg dose and was removed at week 11. In the high-dose arm, the main dose-limiting toxicity was somnolence that required dose reduction in seven patients. The dose was reduced from 800 to 600 mg for five patients and from 800 to 400 mg for two. The other adverse events that did not require dose reduction or removal from the study included the following: constipation, somnolence, fatigue, peripheral neuropathy, dizziness and instability, dry mouth,

skin rash, nausea, anorexia, arrhythmia, neutropenia, headaches, and hypotension (Table 4).

There were five serious adverse event reports during the study. Two patients on the 200-mg dose required hospital admissions for progressive shortness of breath. Both of these patients had progressive increase in pleural effusions that were not related to thalidomide. One patient on the 800-mg dose developed postural hypotension during the first treatment day. She became diaphoretic and light headed but improved rapidly after intravenous fluids were started, and she continued treatment on protocol without similar episodes. Another patient on the 200-mg dose developed dizziness and palpitation, and ECG showed sinus bradycardia with bigeminy that resolved spontaneously. Her echocardiogram was normal, and she continued treatment on the protocol with no similar episodes. The last patient, who was on the 800-mg dose, developed vomiting and headaches that required intravenous hydration at the end of her first day of treatment. She continued on the study with no similar episodes. Although the last three episodes were considered to be probably related to thalidomide, none recurred with continued treatment.

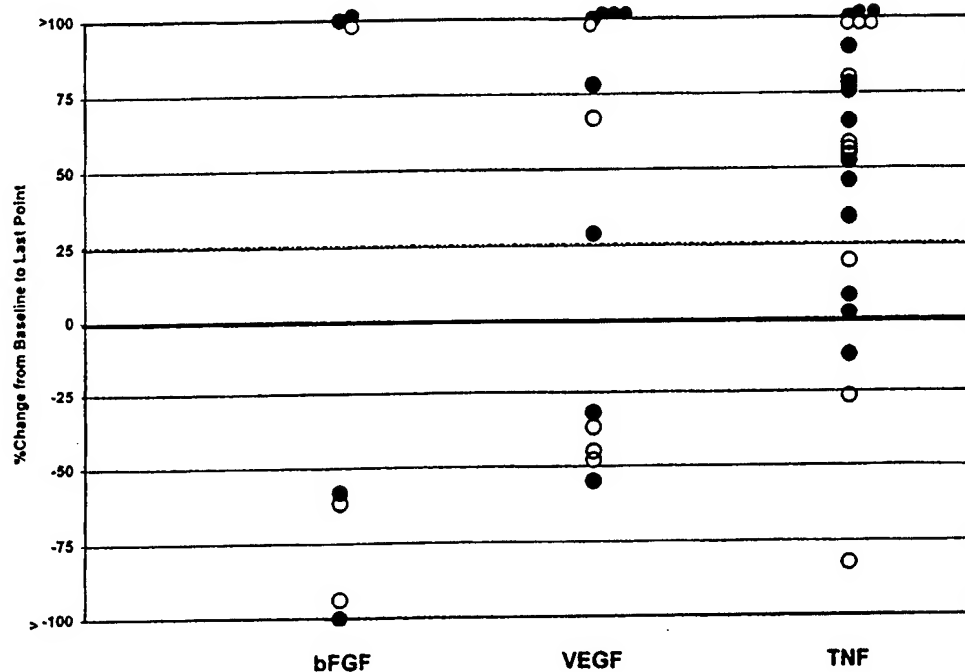
Correlative Studies

Pharmacokinetics. The mean \pm SD steady-state concentration of thalidomide at the 200-mg dose was 1.52 ± 1.1 $\mu\text{g/mL}$ but ranged from 0 to 3.2 $\mu\text{g/mL}$, whereas at the 800-mg dose, the steady-state concentration was 6.2 ± 4.3 $\mu\text{g/mL}$ and ranged from 0.5 to 13.8 $\mu\text{g/mL}$. The mean \pm SD clearance calculated by dividing the dose by the area under the curve over approximately the first 28 hours after the first dose using the trapezoidal method was 5.4 ± 2.4 L/h for the 200-mg dose and 7.7 ± 3.5 L/h for the 800-mg dose. The two doses did not have significantly different oral clearance. These data are consistent with the published data

Table 4. Drug-Related Adverse Events

Adverse Event	200-mg Dose Level (n = 14)		800-mg Dose Level (n = 14)		Total (n = 28)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Constipation	3	21	10	71	13	46
Somnolence	4	29	8	57	12	43
Fatigue	6	43	6	43	12	43
Peripheral neuropathy	5	36	4	29	9	32
Dizziness and instability	2	14	4	29	6	21
Dry mouth	2	14	6	43	8	29
Skin rash	1	7	2	14	3	11
Nausea	0	0	2	14	2	7
Anorexia	1	7	1	7	2	7
Arrhythmia	1	7	0	0	1	4
Neutropenia	1	7	1	7	2	7
Headaches	1	7	1	7	2	7
Hypotension	0	0	1	7	1	4

Fig 1. Changes (%) in circulating bFGF, VEGF, and TNF- α levels from baseline to time of removal from treatment with thalidomide. Symbols: (---), \geq 25% change from baseline level; (●), 800 mg/d; (○), 200 mg/d.



on thalidomide clearance in patients with prostate cancer in which the oral clearance was 7.4 L/h for the 200-mg dose and 7.21 L/h for the 1,200-mg dose and also with data from healthy volunteers.^{37,38}

Circulating angiogenic factor levels. Circulating baseline angiogenic growth factor levels were determined in all but one patient. Of 27 patients, five (18.5%), six (22.2%), and 13 (48.1%) had elevated levels (\geq mean + 1 SD in normal population) of bFGF, VEGF, and TNF- α , respectively. The proportion of patients with elevated TNF- α levels was significantly greater than that for bFGF or VEGF levels ($P = .034$).

Changes in serum bFGF, VEGF, and TNF- α levels from baseline to time of removal from study (either because of progression or toxicity) in 26 patients were determined. One patient did not have baseline specimens collected, and one had baseline but no follow-up specimens collected. The bFGF, VEGF, and TNF- α data are illustrated in Fig 1. Only informative patients were included in this analysis. For bFGF, VEGF, and TNF- α , there were 19, 13, and three noninformative patients, respectively. The data from both dose levels were combined for the paired t test performed on each growth factor. The results of these analyses indicate mean percentage changes from baseline of -37% for bFGF, +60% for VEGF, and +79% for TNF- α . Of these, only the increase in TNF- α levels was statistically significant ($P = .017$).

Of interest, serial changes in circulating levels of bFGF and VEGF seemed random in the single patient who experienced a near-partial response. However, in contrast to all but two other patients, serial TNF- α levels from this patient decreased from baseline to each time point (2, 4, and 8 weeks).

Plasma levels of MMP-2 and MMP-9 were determined by zymography. This method allows the simultaneous measurement of the latent and active forms of the enzyme. Plasma MMP-2 levels remained relatively unchanged over the period of the study. Comparison with the standards revealed that all of the enzyme was apparently in the inactive proform (data not shown). There was considerable variation in the plasma levels of MMP-9 over time, with no discernible, consistent pattern to these alterations (data not shown). Statistical analysis of MMP-9 levels before treatment and at any point during treatment by paired t test did not show any significant trend. Like MMP-2, all of the MMP-9 in patient plasma seemed to be in the inactive proform.

DISCUSSION

In this phase II study of thalidomide in patients with progressive metastatic breast cancer, we have observed little or no activity of thalidomide as a single agent in either the low- or high-dose arm. Two patients on the 200-mg dose level had stable disease at 8 weeks. One patient nearly had

a partial response, with a 43% reduction in the size of mediastinal and hilar lymphadenopathy at 8 weeks, but this disease improvement was short lived. She suffered marked disease progression at week 16, manifested by possible lymphangitic spread, a 200% increase in the mediastinal and hilar lymph node size, and a new suprarenal mass and pleural effusions. The second patient had previously manifested slowly progressing disease over 20 months on no treatment before starting thalidomide. She had stable disease at week 8. She developed grade 3 peripheral neuropathy and was removed from study at week 11. In this case, the observed tumor stability at 8 weeks was more likely a result of a history of indolent disease rather than of thalidomide. Although the protocol stipulated the addition of another 11 patients if one or more patients had stable disease at 8 weeks of treatment in either arm, we elected not to proceed, because 25 of 28 patients had progressive disease at or before 8 weeks of treatment. Furthermore, the two patients who were treated beyond 8 weeks had either short-lived response with rapidly growing disease at week 16 or previously indolent disease. One patient refused to continue treatment beyond 4 weeks because of side effects and refused to have her dose reduced.

Thalidomide was well tolerated at the 200-mg dose level, with only one grade 3 toxicity (peripheral neuropathy). In contrast, the 800-mg dose level was not as well tolerated. The main complaint was somnolence that required dose reduction in seven patients. Although the dose was increased to 1,000 mg in one patient and to 1,200 mg in four patients, those patients complained of early morning somnolence and dizziness that lasted for a few hours. Constipation, dry mouth, and fatigue were common. Nonetheless, at the two dose levels, apart from one patient with grade 3 neuropathy at the 200-mg dose and seven patients with moderate somnolence at the 800-mg dose level, no other symptom required dose modification.

In an effort to gain insight into the mechanism of thalidomide activity, we studied circulating markers of angiogenesis. No identifiable patterns were observed in bFGF and VEGF levels. However, circulating levels of TNF- α significantly increased in most patients during thalidomide treatment. Of note, TNF- α levels decreased in the single patient who experienced a near-partial response, which raises the hypothesis that thalidomide might be active in cancer patients by virtue of decreasing TNF- α . In this regard, prior studies have suggested

that thalidomide is a selective inhibitor of TNF- α in lipopolysaccharide-stimulated monocytes by virtue of degradation of TNF- α mRNA.^{18,19} The capacity of thalidomide to inhibit the production of TNF- α has been described in many diseases, such as chronic graft-versus-host disease, septic syndrome, Bechet's disease, erythema nodosum leprosum, tuberculosis infection, and AIDS. In some studies, serum TNF- α levels decreased during thalidomide treatment in patients with erythema nodosum leprosum and in patients with active tuberculosis.^{39,40} On the other hand, increasing levels of serum TNF- α during thalidomide treatment were observed in human immunodeficiency virus-infected patients with aphthous ulcers.⁴¹

Like bFGF and VEGF levels, serial MMP levels were inconsistent during thalidomide treatment. Determination of MMP levels by gelatin zymography of plasma is semiquantitative at best. Of interest, the identified MMP-2 and MMP-9 enzymes were all in the proform. This observation is in agreement with our previous results.³⁵

The failure of thalidomide in this study was not a result of insufficient blood levels, because most patients achieved detectable plasma levels of thalidomide during treatment. Furthermore, although patients on the 800-mg dose achieved a higher plasma steady-state concentration of thalidomide, no antitumor activity was observed at this dose. The pharmacokinetics data in this study are consistent with the other published data on thalidomide clearance in a group of prostate cancer patients and in healthy normal volunteers.^{37,38}

We conclude that thalidomide has little or no activity as a single agent in this population of patients with previously heavily treated progressive metastatic breast cancer. These results do not preclude activity of thalidomide in other settings, such as in patients with micrometastatic breast cancer or in patients with other types of malignancies. Moreover, they do not preclude possible activity of the drug in combination with other classically active agents, such as hormone therapy or chemotherapy. Likewise, thalidomide might be active with other biologic therapies, such as other inhibitors of angiogenesis or immunomodulators. If such studies are performed, our results suggest that thalidomide might be used at the lower dose levels. The lower dose was better tolerated, and the one near response that was observed was at this dose. Although a few patients tolerated thalidomide at higher doses, the side effects may preclude long-time administration at the dose of 800 mg or more.

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CORE 2
APPENDIX 1.
Outcomes Core Related Publications

Does over-the-counter nicotine replacement therapy improve smokers' life expectancy?

William F Lawrence, Stevens S Smith, Timothy B Baker, Michael C Fiore

Abstract

Objective—To determine the public health benefits of making nicotine replacement therapy available without prescription, in terms of number of quitters and life expectancy.

Design—A decision-analytic model was developed to compare the policy of over-the-counter (OTC) availability of nicotine replacement therapy with that of prescription (R) availability for the adult smoking population in the United States.

Main outcome measures—Long-term (six-month) quit rates, life expectancy, and smoking attributable mortality (SAM) rates.

Results—OTC availability of nicotine replacement therapy would result in 91 151 additional successful quitters over a six-month period, and a cumulative total of approximately 1.7 million additional quitters over 25 years. All-cause SAM would decrease by 348 deaths per year and 2940 deaths per year at six months and five years, respectively. Relative to R nicotine replacement therapy availability, OTC availability would result in an average gain in life expectancy across the entire adult smoking population of 0.196 years per smoker. In sensitivity analyses, the benefits of OTC availability were evident across a wide range of changes in baseline parameters.

Conclusions—Compared with R availability of nicotine replacement therapy, OTC availability would result in more successful quitters, fewer smoking-attributable deaths, and increased life expectancy for current smokers.

(*Tobacco Control* 1998;7:364-368)

Keywords: smoking cessation, nicotine replacement therapy, over-the-counter sales, decision analysis

polacrilex gum).⁵⁻⁷ Although smoking cessation programmes are more efficacious than self-quitting, considerable evidence suggests that most smokers are reluctant to participate in cessation programmes.⁸⁻¹⁰ This suggests that making nicotine replacement products available outside formal cessation programmes may increase smoking cessation rates among American smokers. One strategy to make nicotine replacement products more available to self-quitters is to make them available over the counter (OTC).^{11 12}

In July 1996, the FDA first approved over-the-counter sales of one brand of nicotine patch.¹³ The patches appear to be a popular cessation aid; by the end of 1996, one brand of OTC nicotine patch, Nicoderm CQ, had sold over 3.2 million units (unpublished data, SmithKline Beecham, Inc.). Use of nicotine replacement therapy has been estimated to increase by over 150% since nicotine patches and nicotine gum have become available without prescription.¹⁴ An accurate estimate of the potential public health benefits of the policy of making nicotine replacement available without prescription depends upon formal analysis that models the anticipated benefit based upon specific, empirically derived assumptions. The current study used decision-analytic techniques to compare the public health impact of prescription with over-the-counter nicotine replacement therapy availability. The analyses used data on the estimated percentage of American smokers who would quit successfully per year, and on estimated reductions in smoking-attributable mortality, derived from sources available before nicotine replacement was available OTC in the United States, or from post-marketing surveillance after nicotine replacement was available without prescription.

Methods

We constructed a simulation model¹⁵ using a computer spreadsheet (Microsoft Excel for Windows version 5.0, Microsoft Corporation, Redmond, Washington) to compare the public health impact of making nicotine replacement therapy (NRT) by transdermal patch or by nicotine polacrilex gum available over the counter (OTC scenario) with the practice of prescription-only availability (R scenario). We used data from non-prescription availability Nicoderm patch studies conducted by Alza Corporation as proxy for over-the-counter nicotine replacement in general, due to the availability of over-the-counter data for this particular product. Outcomes determined for

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Introduction

Smoking cessation and prevention strategies hold tremendous potential to improve public health.¹ Smoking-attributable mortality is now estimated at more than 400 000 deaths per year and the health benefits of quitting at any age have been well documented.² Although over 70% of smokers would like to quit smoking,³ less than 5% of self-quitters successfully stop smoking for six months or more,⁴ a figure considerably lower than the 10-30% quit rates produced by smoking cessation programmes using prescription (R) nicotine replacement products (transdermal patches or

Table 1 Model parameters

Parameter	Value*	Sources
OTC scenario		
Probability of using NRT if attempting to quit	0.35	8, 14
Probability of quitting six months using NRT†	0.106	19
R _x Scenario		
Probability of using NRT if attempting to quit	0.14	8‡
Probability of quitting six months using NRT†	0.106	19
Both scenarios		
Probability of attempting to quit by any method	0.31	17§
Probability of quitting six months for those attempting without NRT†	0.049	4, 24
Markov models		
One-year probability of relapse for quitters in first two years	0.11	2¶
One-year probability of relapse for long-term quitters	0.024	2¶
Relative risk of death, current smoker to former smoker (age 18–29 years)	1.0	**
Relative risk of death for current smoker to former smoker (age ≥ 30 years)	Age and sex dependent (range: 1.2–2.5)	1, 17, 23††
One-year probability of death, former smoker	Age and sex dependent (range: 0.0051–0.18)	16

OTC = over the counter; NRT = nicotine replacement therapy.

*Values for table 1 are presented as the weighted average of values across age and sex strata.

†Based on self-reported continuous quit rates in OTC setting; see text.

‡Based on all reported NRT use (patch and gum) from Pierce *et al.* [8]

§Based on the 1992 National Health Interview Survey data from the National Center for Health Statistics on CD-ROM. These estimates were computed by Dr SS Smith, who is solely responsible for the accuracy and appropriateness of the calculations.

¶Estimates were based on two stage DEALE transformations [14] to estimate yearly relapse transition probabilities for short-term (1–2 year) and long-term quitters based on National Health and Nutrition Examination Survey data.

**No data were available for this age group, so we used a conservative assumption that the mortality was not increased in current smokers relative to former for those less than 30 years old.

††Estimates were derived from the Cancer Prevention Study II (CPS-II), using the above sources, as well as unpublished CPS-II data provided by MJ Thun (personal communication). Data are stratified by age and sex, but are independent of duration of abstinence for former smokers.

both the OTC and R_x scenarios included: (a) the total number of smokers who quit at six months; (b) overall smoking-attributable mortality; and (c) life expectancy of an average smoker using state-transition (Markov) modelling.

DATA SOURCES

Modelling required estimates derived from diverse sources. A MEDLINE literature search was conducted for relevant literature on model parameters. Whenever possible, effectiveness data was preferentially chosen over efficacy data. Population estimates were based on 1990 census data.¹⁶ In addition, several national sur-

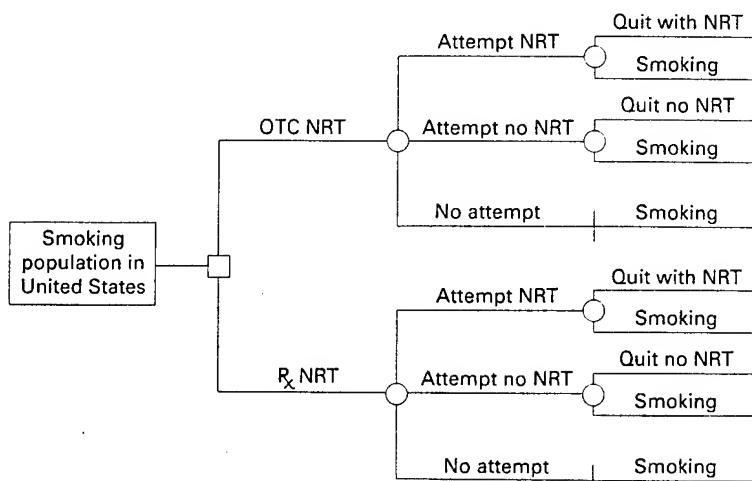


Figure 1 Decision tree for determining the public health benefits of the two scenarios of availability of nicotine replacement therapy. Public health benefits shown in the tree include the number of quit attempts and the number of long-term (six-month) quits. NRT = nicotine replacement therapy, OTC = over the counter, R_x = prescription.

veys were used to provide population-based estimates, including the 1990 and 1992 National Health Interview Surveys,^{17, 18} (NHIS) to provide estimates of smoking prevalence and smoking cessation attempts, and the National Health and Nutrition Examination Survey-I (NHANES-I) and the NHANES Epidemiologic Followup Survey² to provide the probability of smoking relapse.

Estimates of the rate of use of nicotine replacement in the OTC scenario were based on marketing surveillance of nicotine replacement therapy use, performed by Shiffman and colleagues.¹¹ These investigators determined the ratio of use of nicotine products for non-prescription availability compared with prescription availability. We used this ratio multiplied by our estimates for prescription use of nicotine replacement therapy to calculate the rates of use in the over-the-counter setting.

Smoking cessation rates for NRT quitters under both scenarios were derived from a prospective trial of simulated non-prescription nicotine patch use.¹⁹ As noted, we use nicotine patch data as a proxy for nicotine replacement therapy in general, due to the availability of the data on over-the-counter use for this form of replacement. A prospective cohort study was conducted using 2367 participants recruited from public locations such as shopping malls; participants purchased patches at estimated retail price, and were followed up to determine quit rates. Participants lost to follow up in this study were considered to have relapsed. We assume for this analysis that the six-month quit rates for smokers using nicotine replacement was equivalent in the OTC and R_x scenarios. Post-marketing surveillance using retrospective cohort data on prescription nicotine patch use¹⁹ suggests that the six-month quit rate may actually be lower in the prescription setting. Thus, this assumption is a conservative one which will bias the analysis in favour of the prescription scenario by underestimating the over-the-counter public health benefit. We examine changes in this assumption in sensitivity analysis.

Whenever possible, age-specific and sex-specific data were used in the model. All quit rates are based upon self-reported continuous quit rates which were the most consistently available data. Table 1 provides a summary of parameters used for the baseline case for the model. (Parameter estimates stratified by age and sex from these studies are available in a technical report available on request from the authors.)

THE DECISION MODEL

A decision tree was constructed (figure 1) to estimate the number of current smokers who would quit long-term (six months) in the OTC and R_x scenarios for each age and sex stratum. In both scenarios, a smoker has a chance of making a quit attempt using nicotine replacement therapy, a chance of making a quit attempt without nicotine replacement, and a chance of not making a quit attempt. We assume for the baseline analysis that the total

Table 2 Baseline results

	R Scenario*	OTC Scenario†
Number of adult smokers in the United States	47 002 476	47 002 476
Number willing to try NRT per year	1 014 630	2 556 867
Willing to try NRT per year (%)	2.2	5.4
Quit rate of smokers using NRT at six months (%)	10.8	10.8
Number of quits using NRT at six months	109 685	276 405
Gain in number of quits for OTC scenario at six months	NA	91 151
Total number of quits at six months	420 330	511 480
Life expectancy of average smoker (years)	34.211	34.407
Gain in life expectancy for average smoker (years)	NA	0.196
Smoking-attributable mortality rate (based on six-month data) (deaths per year)	412 617	412 269
Reduction in smoking-attributable mortality rate (based on six-month data) (deaths per year)	NA	348 (0.1%)
Reduction in smoking-attributable mortality rate for OTC scenario (based on five-year data) (deaths per year)	NA	2940 (0.7%)

*Nicotine replacement therapy (NRT) available only by prescription.

†Nicotine replacement therapy available over the counter (OTC).

NA = not applicable.

chance of making a quit attempt by any method is the same for both scenarios. We also assume that any patterns in changes of use of other smoking cessation methods, such as behavioural counseling, would not significantly affect cessation rates for smokers quitting without nicotine replacement in either scenario of nicotine replacement availability. Both of these assumptions were examined in sensitivity analysis.

Markov state-transition models²⁰ were created to estimate the life expectancy of an average person in each stratum. Each model consisted of five states, representing: current smokers; those quitting for a year or less; those who have quit for one to two years; long-term quitters; and those who have died. These state transition models represent each smoker in the simulation as being in one of the five mutually exclusive states for any particular one-year period. Probabilities were calculated for a person in one state (for example, long-term quitter) to transition to any other state (such as smoking) in the following year. The three quit states allow representation of a lower relapse rate for longer term quitters (more than two years) compared with more recent quitters.² Mortality for current and former smokers was

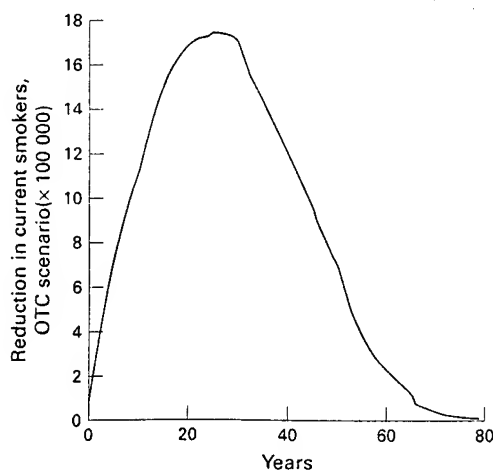


Figure 2 Reduction in the number of smokers in the over-the-counter (OTC) scenario compared with the prescription (R) scenario, over time. The reduction is based on the difference in current smokers between the two scenarios, adjusted to the population size of the OTC scenario, for the original cohort of 47 million adult smokers.

stratified by age and sex,^{18,21} however, data were not available to calculate this parameter for duration of cessation, so rates are independent of duration of abstinence for former smokers.

For each age and sex stratum, the initial distribution of cohort members across the states was determined by the outcome of the decision tree for that stratum. The model calculated life expectancy until the surviving members of the cohort reached age 100. Transition probabilities for the Markov models were age and sex dependent.

Results

BASELINE RESULTS

Major outcomes of the analysis are shown in table 2. Key findings are that making nicotine therapy available over the counter would result in approximately 1.1 million additional smokers attempting to quit using nicotine replacement therapy in the first six months, and an estimated 91 151 additional smokers would have quit at the end of six months. The number of additional quitters from the current cohort of smokers would continue to increase over time to a maximum of 1.7 million additional quitters at 25 years in the OTC scenario compared with the R scenario (figure 2).

Reclassifying nicotine therapy as non-prescription would also have a positive impact on life expectancy. Across the total cohort of more than 47 million smokers (including continuing smokers and eventual quitters), the average smoker could be expected to live 0.20 years (2.4 months) longer in the over-the-counter scenario than in the prescription scenario (table 2). The impact of permanently quitting smokers on gain in life expectancy on successful quitters is presented in table 3. On average, each of these new quitters will gain an average of 4.4 years of life compared with smokers who never quit. Thus, the average gain in life expectancy represents a large life expectancy gain that accrues to the small percentage of smokers who would quit in the non-prescription availability setting but not in the prescription setting.

Based on the proportion of quitters at six months in the OTC scenario compared with that in the R scenario, we estimated a reduction in the all-cause, smoking-attributable mortality rate of 348 deaths per year. At five years, our model predicts a decrease in the all-cause, smoking-attributable mortality rate of 2940 deaths per year for the over-the-counter scenario, due to the increased

Table 3 Gain in life expectancy* for smokers who successfully quit smoking

Age	Men	Women	Total
18-24	6.30	4.01	5.28
25-44	5.85	3.78	4.92
45-64	4.26	3.43	3.86
≥65	1.91	1.33	1.59
Total	5.22	3.47	4.41

*Gain in life expectancy (years) for individual smokers who successfully and permanently quit smoking today, compared with smokers who continue to smoke for the rest of their lives. Totals represent average life expectancy weighted by the number of people in each age and sex stratum.

Table 4 Sensitivity analyses

Parameter*	Gain in number of quits at six months (OTC scenario)	Gain in life expectancy† (OTC scenario)
Baseline	91 151	0.196
Change in probability of attempting to quit by any method (baseline average = 0.31)‡		
0.75 *baseline (average = 0.23)	68 363	0.163
1.25 *baseline (average = 0.39)	113 939	0.222
Two quit attempts per year for those attempting to quit by any method (baseline = 1 per year)	180 661	0.266
Relative chance of quit attempt by any method, OTC to R (baseline 1 to 1):		
0.9 to 1	40 003	0.108
1.1 to 1	142 299	0.280
1.3 to 1	244 595	0.437
Threshold value§: 0.79 to 1		
Probability of using NRT should a quit attempt be made (both scenarios; baseline average = 0.14 R, 0.36 OTC)‡		
0.5 *baseline (average = 0.07 R, 0.18 OTC)	45 576	0.104
0.75 *baseline (average = 0.11 R, 0.27 OTC)	68 363	0.152
1.25 *baseline (average = 0.18 R, 0.45 OTC)	113 939	0.238
Threshold value§: 0		
Relative chance of using NRT for those quitting in OTC scenario compared with chance of using NPT in R scenario (baseline average = 2.52 to 1)‡		
0.5 *baseline (average = 1.26 to 1)	15 592	0.035
0.8 *baseline (average = 2.02 to 1)	60 927	0.133
1.2 *baseline (average = 3.02 to 1)	121 375	0.257
Threshold value§: 0.40; *baseline (average = 1 to 1)		
Probability of a successful quit at six months for those attempting with NRT in the R scenario (OTC scenario probabilities held constant; baseline average = 0.106)‡		
1.25 *baseline (average = 133)	63 730	0.137
1.5 *baseline (average = 0.159)	36 309	0.080
2.0 *baseline (average = 0.212)	(18 534)	(0.029)
Threshold value§: 1.86; *baseline (average = 0.197)		
Probability of a successful quit at six months for those attempting with NRT in the OTC scenario (R scenario probabilities held constant; baseline average = 0.106)‡		
0.5 *baseline (average = 0.053)	(47 052)	(0.096)
0.75 *baseline (average = 0.080)	22 050	0.055
1.25 *baseline (average = 0.133)	160 252	0.326
Threshold value§: 0.66 *baseline (average = 0.070)		
Probability of a successful quit at six months for those attempting with NRT (baseline average 0.106 R, 0.106 OTC)‡		
1.2 *baseline in R scenario (average = 0.127) and, 0.8 *baseline in OTC scenario (average = 0.084)	13 933	0.037
Probability of a successful quit at six months for those attempting without NRT (baseline average = 0.049)‡		
0.8 *baseline (average = 0.039)	106 265	0.235
1.2 *baseline (average = 0.059)	76 037	0.160
2.0 *baseline (average = 0.098)	15 581	0.040
Threshold value§: 2.3; *baseline (average = 0.113)		
Probability of a successful quit at six months for fraction of those attempting without NRT but with non-pharmacological therapy in OTC scenario (baseline average = 0.049)‡		
0.75 *baseline (average = 0.037)	32 382	0.115
0 *baseline (average = 0)	(143 924)	(0.150)
Threshold value§: 0.41 *baseline (average = 0.020)		

NRT = nicotine replacement therapy; OTC = over the counter, R = prescription.

*Changes in parameters noted as a multiplier; *baseline represents the values of the parameter across age and sex strata multiplied by the number to achieve the result listed.

†Measured in average years of life gained for an individual smoker.

‡The weighted average is the average of the values across age and sex strata adjusted to the American adult smoking population. These numbers are provided for reader reference; the analyses were performed using adjustment of each of the strata by the multiplier listed.

§The threshold value is the value of the parameter at which the life expectancy is equal in both the R and the OTC scenarios.

number of quitters in this scenario compared with the prescription scenario (table 2). For the original cohort of 47 million smokers, this gap between the smoking attributable mortality in the non-prescription setting and the prescription setting would continue to widen for approximately 30 years.

SENSITIVITY ANALYSES

Results of the sensitivity analyses demonstrated that the model results were robust for a wide range of changes in the baseline parameters (table 4). The results were most sensitive to changes in the parameter values of the relative chance of making a quit attempt by any method, and the relative probabilities of a successful quit at six months for the OTC and R scenarios. If, for example, the smokers are 10% more likely to attempt to quit by any method in the OTC scenario compared with the R scenario, then the gain in number of quits at six months for the OTC scenario increases by 56% over baseline, and the gain in life expectancy for the OTC scenario increases

by 43%. Conversely, if either the chance of a successful quit at six months is either twice what we predict for the R scenario, or a half of what we predict for the OTC scenario, then the R scenario has more quitters and a better life expectancy.

Threshold values from the sensitivity analyses are also shown in table 4. Threshold values are the values of the model parameters at which there is no longer a life expectancy benefit for smokers in the non-prescription scenario compared with the prescription scenario. For example, if smokers were only 79% as likely (or less) to attempt to quit by any method in the OTC scenario compared with the R scenario, then the OTC scenario would not have a life expectancy advantage.

Discussion

Smoking is a major source of morbidity and mortality in the United States. Thus, policies that even modestly improve smoking cessation rates have the potential to yield large public health benefits. In this analysis, we show that

making nicotine replacement therapy using transdermal patches and nicotine gum available over the counter rather than prescription-only would result in a large increase in the number of successful quitters each year, a reduction in smoking-attributable mortality, and an increase in the life expectancy of smokers. The gain in life expectancy for an average smoker in the over-the-counter setting is 0.196 years; in comparison, the gain in screening 40-year-old men and 40-year-old women for hypertension would be an increase in life expectancy of 0.03 years and 0.01 years, respectively.²²

Sensitivity analyses demonstrate that the over-the-counter use has a relative benefit compared with prescription use under a wide variety of assumptions. Perhaps the area of greatest uncertainty within the analysis is the six-month effectiveness data for both prescription and non-prescription nicotine replacement therapy. Data are available on NRT-assisted quit rates⁵; these represent primarily efficacy results of clinical trials. In contrast, the analyses in this model used data estimating effectiveness of nicotine replacement under the OTC scenario. Surveillance data suggest that effectiveness of prescription-only patch use may have a 40% lower six-month success rate than we use for the baseline model.¹⁹ Potential quitters willing to use NRT as an over-the-counter medication may, on average, have fewer or less severe factors for relapse.²³ In contrast, smokers who seek cessation services (including NRT) through health-care providers may, on average, include people with a greater number or level of relapse risk factors.¹⁰ If the six-month cessation rate for prescription use nicotine therapy is lower than we have estimated, then the actual benefits would be greater than we have calculated. Even if the six-month cessation rates for non-prescription nicotine replacement therapy use are 20% worse than we have estimated, and that of the prescription nicotine replacement use 20% better than estimated, our model still predicts a small benefit for the non-prescription availability setting.

There are several caveats that should be considered when evaluating our results. First, there are no randomised clinical trial data linking NRT-based smoking cessation programmes to overall reduction in mortality. Next, we do not explicitly address the issue of adverse effects of nicotine replacement. Since the analysis only addresses mortality associated with smoking, we did not include adverse effects because death directly attributable to NRT therapy itself is an exceedingly rare event, and thus would not change the results of the analysis. Other adverse effects of nicotine replacement therapy—for example, skin irritation from the transdermal patch—tend to be transitory and produce little impact on overall health. Finally, we do not address the economic impact of making nicotine replacement available without prescription.

Overall, we have found that making nicotine replacement therapy available without prescription would result in substantial public

health benefit. By implementing a policy to make nicotine patches and gum available as over-the-counter medications for smoking cessation, the number of current smokers would significantly decrease over time, and smoking-attributable mortality would decline as well.

This study was funded by a grant from SmithKline Beecham. Dr Lawrence is supported in part by Contract DAMD 17-96-C-6069, "Breast Cancer Support Contract," from the Department of the Army. Dr Fiore has done consulting and public speaking for the following pharmaceutical companies: SmithKline Beecham, Ciba-Geigy, McNeil, and GlaxoWellcome.

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ARTICLES

Serendipity in Diagnostic Imaging: Magnetic Resonance Imaging of the Breast

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Matthew Freedman, Susan M. Ascher, Bruce J. Trock, Polun Chang

Background: Magnetic resonance imaging (MRI) of the breast has been proposed as a noninvasive diagnostic test for evaluation of suspicious ("index") lesions noted on mammography and/or clinical breast examination (CBE). However, women may have incidental ("serendipitous") lesions detected by MRI that are not found on mammography or CBE. To understand better whether or not biopsy procedures should be performed to evaluate serendipitous lesions, we estimated the breast cancer risk for women with this type of lesion. **Methods:** A decision analysis model was used to estimate the positive predictive value (i.e., the chance that a woman with a serendipitous lesion has cancer) of MRI for serendipitous lesions in women who had an abnormal mammogram and/or CBE suspicious for cancer (where a biopsy procedure is recommended). We restricted the analysis to data from women whose index lesions were noncancerous and used meta-analysis of published medical literature to determine the likelihood ratios (measures of how test results change the probability of having cancer) for MRI and the combination of CBE and mammography. The positive predictive value of MRI was calculated using the U.S. population prevalence of cancer (derived from registry data) and the likelihood ratios of the diagnostic tests. **Results:** Under a wide variety of assumptions, the positive predictive value of MRI was extremely low for serendipitous lesions. For instance, assuming sensitivity and specificity values for MRI of 95.6% and 68.6%, respectively, approximately four of 1000 55- to 59-year-old women with serendipitous lesions would be expected to have cancer (positive predictive value = 0.44%, 95% confidence interval = 0.24%–0.67%). **Conclusion:** In women with a suspicious lesion discovered by mammography and/or CBE that is found to be benign, serendipitous breast lesions detected by MRI are extremely unlikely to represent invasive breast cancer. Immediate biopsy of such serendipitous lesions may, therefore, not be required. [J Natl Cancer Inst 1998;90:1792–800]

Mammography and clinical breast examination (CBE) are the current standard measures for breast cancer screening and initial evaluation of breast signs and symptoms. The combination of mammography and CBE has a moderate sensitivity and high specificity for breast cancer. However, the positive predictive value of these tests for cancer, especially when done for screening and in young women, may be quite low, due to a low prior

probability of cancer. For example, in a large Canadian screening study, only 12% of women aged 40–49 years who were recommended to have a biopsy procedure as a result of an abnormal screening mammogram or CBE actually had breast cancer (1). An estimated 600 000 breast biopsies are performed annually in the United States (2); as many as 85% of these yield benign results (3–6). Thus, the potential economic and quality-of-life (7–12) impact of alternative diagnostic pathways could be substantial.

To reduce the number of biopsies performed on women who will ultimately be diagnosed with benign lesions, several intermediate diagnostic tests have been proposed (13,14). Such tests would need to have high sensitivity, so that there are few missed cancers, and ideally also have high specificity, so that women without breast cancer would not be required to undergo an unnecessary invasive procedure.

One test currently under investigation as an intermediate diagnostic test is magnetic resonance imaging (MRI) of the affected breast. Studies suggest that MRI will be quite sensitive but may not be very specific, with specificity as low as 30% (15). Also, MRI of the breast has been reported to show breast lesions not found on either the initial mammogram or CBE. We refer to these lesions as "serendipitous lesions"—lesions found incidentally in the work-up of another breast lesion (16). These lesions raise a diagnostic dilemma: If the MRI has a higher sensitivity than conventional procedures, then cancer, if present, would be more likely to be detected by the MRI than the mammogram; on the other hand, if the specificity is truly much lower, then these serendipitous lesions are much more likely to be false-positive lesions than if they were originally found on mammography or CBE. In addition, localizing these lesions for biopsy procedure would be quite difficult if other diagnostic modalities cannot detect them; in this case, an MRI-guided biopsy procedure may be necessary to ensure localization of the lesion.

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If the suspicious lesion that prompted MRI evaluation is found to be benign, what should be done diagnostically to evaluate these serendipitous breast lesions found on MRI? Using decision analysis and the best estimates from a comprehensive literature review, we estimate the positive predictive value of these serendipitous lesions found on MRI or the probability that women with serendipitous lesions truly have invasive breast cancer. These data, while preliminary, provide clinicians and patients with a framework for deciding on the appropriate work-up of unexpected breast lesions found by MRI.

METHODS

There are no published data that specifically address the question of risk of cancer in a serendipitous MRI lesion detected in the course of diagnostic evaluation of another abnormality on mammogram and/or CBE (the "index lesion"). We restrict our analysis to the situation where the index lesion is not malignant and calculate the probability that a woman with a serendipitous lesion has cancer based on biopsy results for the index lesions, age, race, and degree of cancer risk. Women with malignant index lesions are excluded from this analysis.

Decision Model

We used standard decision-analytic techniques (17) to model the sequence of events leading to the finding of a serendipitous lesion on MRI of the breast and to estimate the probability of cancer in the serendipitous lesion. We used a computer spreadsheet (Microsoft Excel v. 5.0 for Windows; Microsoft, Inc., Redmond, WA) for model construction.

As noted above, we define the index lesion as the lesion found on mammogram and/or CBE that prompted a recommendation for biopsy procedure and further evaluation. A serendipitous lesion represents a lesion seen on MRI that was not suspected by either the index mammogram or CBE.

The conceptual approach to the construction of the model is shown in Fig. 1. A woman having a biopsy procedure for the index lesion will either have a benign or a malignant lesion. We assume that if the index lesion is malignant, the clinician may wish to pursue the serendipitous lesions for the possibility of a multicentric cancer, and these women are excluded from this analysis. If the woman has an index lesion that is benign, we assume that her initial probability of cancer is the U.S. population average for her age and race. We also assume that the woman does not have a personal history of breast cancer; this history could raise her initial probability of disease. By definition, the mammogram and the CBE for this woman were negative in the area of the serendipitous lesion, which lowers the probability of cancer. Her probability of cancer given these prior negative tests is calculated using a Bayesian revision of probability (17) and is influenced by her probability of cancer before the test and the sensitivity and specificity of the index mammography and CBE. The positive MRI raises her probability of cancer; this probability is affected by the sensitivity and specificity of MRI. Thus, overall, our model calculates the probability of cancer given the positive MRI, a negative mammogram and CBE, and the initial probability of disease for women of different ages and races.

Model Parameters

We estimated three parameters for this model: the likelihood ratio positive of MRI, the likelihood ratio negative of the combination of mammography and CBE, and the initial prevalence of breast cancer. The likelihood ratio positive is the ratio of sensitivity to one minus the specificity and represents the degree to which a positive test raises the odds of diagnosis. The likelihood ratio negative is the ratio of one minus the sensitivity to specificity and represents the degree to which a negative test lowers the probability of disease. Meta-analyses were conducted to estimate the likelihood ratios of MRI and mammography and CBE. Meta-analysis is a technique that can be used to summarize the results of good-quality studies (18-23) performed in diverse settings and populations. Such analyses are useful for new diagnostic tests, such as MRI, when no one study has sufficient power to address a particular question, and for summarization of the data across multiple studies on potentially different populations with different diagnostic thresholds for a positive test.

Sensitivity and specificity of MRI. Data for the sensitivity and specificity of breast MRI, used to calculate the likelihood ratio positive, came from the pub-

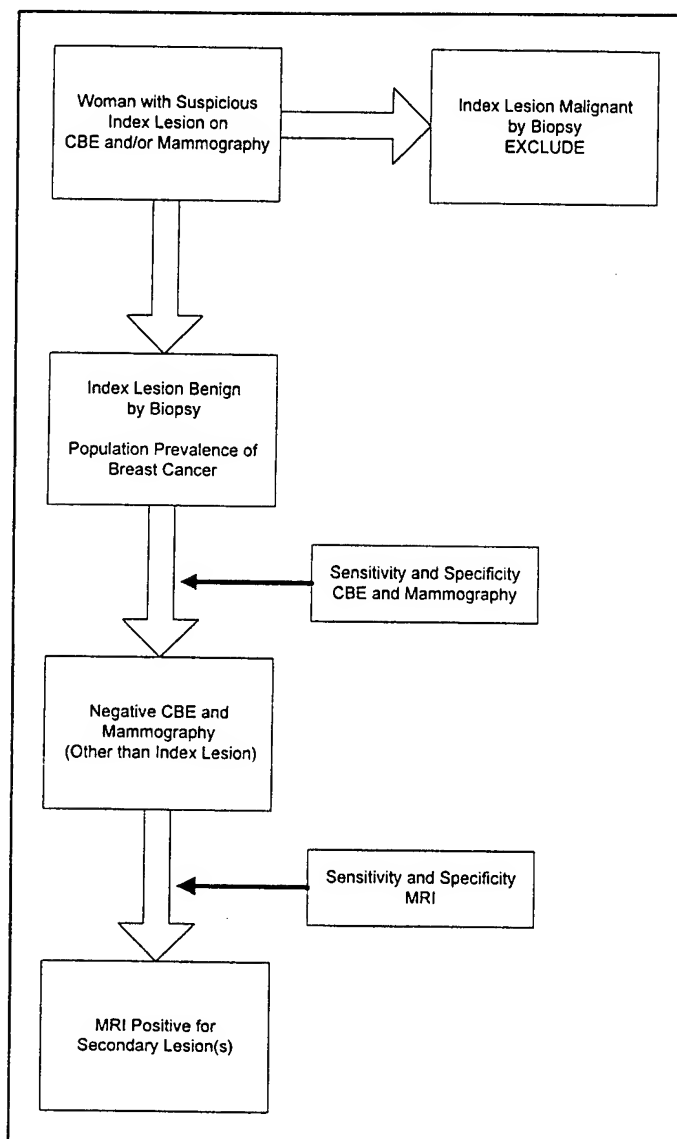


Fig. 1. Algorithm for calculating the positive predictive value of serendipitous breast magnetic resonance imaging (MRI) lesions. CBE = clinical breast examination.

lished medical literature. We performed a MEDLINE® (National Library of Medicine) search, from 1990 through 1997, using the terms "magnetic resonance imaging" and "breast neoplasms." We also searched references of relevant articles. Inclusion criteria for the abstraction of data from an article included the following: 1) sample size of 10 or greater; 2) data were available on MRI and breast cancer results; 3) the study sample consisted of women at risk for cancer, defined as having a suspicious finding on CBE and/or mammogram, but without known cancer at study entry; 4) the MRI readers were blinded to the final diagnosis; and 5) the article was written in English. We did not exclude articles in which the MRI readers had access to mammography or clinical examination data, since we assumed that in clinical practice the MRI reader would review these data when reading the MRI. For studies eligible for inclusion, the following data were abstracted: study design; patient selection; number and age of subjects; method for MRI; method for diagnosing breast cancer; and numbers of true-positive, false-positive, true-negative, and false-negative MRI results. Although this study is concerned with the diagnosis of invasive breast cancer, we include the diagnosis of ductal carcinoma *in situ* (DCIS) as a true-positive diagnosis for the purposes of calculating the sensitivity and specificity of MRI. This assumption results in a higher positive predictive value of MRI than would not including DCIS as a true-positive result; assuming otherwise would result lower the specificity of MRI, lowering the positive predictive value. Data could

not be found on the diagnostic accuracy of MRI in specific areas of the breast where the mammogram and CBE were negative. Thus, we assume that the sensitivity and specificity of MRI for the detection of breast cancer are the same for serendipitous lesions as they are for index lesions. Given the paucity of age-specific data, we also assume that the diagnostic accuracy of MRI is independent of age.

Sensitivity and specificity of mammography and CBE. Data for the diagnostic characteristics of CBE and mammogram were derived from the four major randomized trials of breast cancer screening that employed both CBE and two-view mammography (1,24-26). Although only one of these studies was conducted in the United States, we assume that the sensitivity and specificity of mammography and CBE are independent of the country in which the study was performed. Similar to MRI, data from these studies were abstracted to define true-positive, false-positive, true-negative, and false-negative results. We used the detection method (27) to calculate sensitivity of mammography and CBE. True positives were defined as screening-detected cancers, whether found by mammogram, CBE, or both. False negatives were defined as those who were diagnosed as having breast cancer in the interval between screening tests. False positives were defined as those participants undergoing biopsies for benign lesions. True negatives were those who did not clinically develop cancer during the study follow-up period. While probably not strictly true (28), we make the simplifying assumption that CBE and mammography combined test accuracy is independent of age. We examine this assumption in sensitivity analysis by calculating the effects of lower sensitivity for mammography and CBE for women under 50 years of age. While mammography may be less sensitive in this age group, these women also have a low prior probability of cancer. We also assume that the diagnostic accuracy of CBE and mammography is conditionally independent of that of MRI, conditioned on the presence or absence of cancer (29). Thus, for example, if a woman has cancer and a positive MRI, her probability that the CBE and/or mammogram are positive is the same as it would be if she had cancer but a negative MRI.

Breast cancer prevalence. Yearly incidence rates of breast cancer will underestimate breast cancer prevalence since not all breast cancer will be detected in the year following the onset of the cancer. Data for the baseline prevalence of undiagnosed breast cancer in the U.S. population were derived from a simulation model of the natural history of breast cancer (30,31). This model uses breast cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER)¹ registry (32) as well as U.S. population data (33) to estimate the prevalence of cancer by age, race [as reported by Ries et al. (32): black, white, and total population], and incidence rate. We estimate prevalence of invasive breast cancer only; our data do not include the prevalence of DCIS in the population. Data from this model have been validated against Wisconsin and Iowa tumor registry data (30). That model was used to calculate a ratio of detected disease to undetected disease. Using this ratio, we then estimated the age- and race-specific prevalence of disease. We also calculated prevalences for "high-risk" women, using twice the average U.S. population incidence rates to represent those at high risk. We use this high-risk estimate to approximate the increased risk of having a first-degree relative with breast cancer (34-41) or of having previously had a biopsy showing benign breast disease (42-45).

Analysis

Meta-analysis. Using data from the literature of the sensitivity and specificity of the tests, we converted these data into likelihood ratios and pooled the data across studies using an analogue of a Mantel-Haenszel estimator. We use the ratio of the average sensitivities and complements of specificities to preserve the roles of the sensitivity and specificity in the calculation of the likelihood ratio in the estimator, and because this estimator is the closest analogue of the Mantel-Haenszel estimator of odds ratios (46). The estimator for the likelihood ratio positive for MRI (LR_{MRI+}) was calculated using the formula:

$$LR_{MRI+} = \frac{\sum_{i=1}^{12} \frac{TP_i}{TP_i + FN_i}}{\sum_{i=1}^{12} \left[1 - \frac{TN_i}{TN_i + FP_i} \right]} \quad \text{sensitivity} \quad (1 - \text{specificity})$$

where TP_i is the number of true-positive diagnoses for study i , FN_i is the number

of false negatives, TN_i is the number of true negatives, and FP_i is then number of false positives. The likelihood ratio negative for the combination of mammography and CBE ($LR_{MAM,CBE-}$) was calculated in a similar fashion (see below). We obtained the 95% confidence intervals (CIs) by using jackknife estimation and recalculating likelihood ratios, leaving one study out for each study in the analysis (47). The standard errors (SEs) of the means of the likelihood ratios (LR s) were calculated using the following formula:

$$SE = \sqrt{\frac{n}{n-1} \times \sum_{i=1}^n [LR_i - \overline{LR}]^2}$$

where n is the number of studies in the analysis, and LR_i is the recalculated likelihood ratio leaving out study i . The 95% CIs were then calculated by:

$$95\% \text{ CI} = \overline{LR} \pm 1.96 \times SE.$$

Independent estimation of sensitivity and specificity of a diagnostic test using Mantel-Haenszel meta-analytic methodology may underestimate true sensitivity and specificity (48). Thus, we performed the meta-analysis on the likelihood ratios, to recognize the interdependence of these two measures of accuracy. Since underestimation of the sensitivity and specificity of MRI would result in an underestimation of the probability of disease given a positive MRI, we also examined the sensitivity and specificity of this test using the technique of the summary receiver-operating characteristic curve (48). This technique creates a receiver-operating characteristic (ROC) curve based on sensitivity and specificity data from multiple studies. This technique has the advantage, similar to our method of estimating likelihood ratios, of recognizing the interdependency of sensitivity and specificity. We also use this technique to test for homogeneity of the different MRI studies, looking for outliers on the summary ROC curve.

Positive predictive value of MRI. The probability of having cancer given a negative mammogram and CBE but positive MRI (the post-test probability) was calculated using the following equations:

$$\text{Post-test odds} = \text{pre-test odds} \times LR_{MAM,CBE-} \times LR_{MRI+}$$

where

$$\text{Pre-test odds} = \frac{\text{pre-test probability}}{1 - \text{pre-test probability}}$$

and post-test odds are converted to probability using the formula:

$$\text{Post-test probability} = \frac{\text{post-test odds}}{1 + \text{post-test odds}}$$

The post-test probability represents the positive predictive value of MRI given that the mammogram and CBE were negative in the area of the suspicious lesion found on MRI. We use a person-level analysis to calculate the positive predictive value of MRI as opposed to a lesion-level analysis; thus, the positive predictive value represents the probability that the woman has cancer given an MRI finding of a serendipitous lesion or lesions.

Monte Carlo simulations. We use Monte Carlo (49) stochastic simulations to calculate two-sided CIs for the positive predictive value of MRI, given starting age, race, and given that the mammogram, CBE, and index lesion biopsy are negative. In this simulation technique, each uncertain parameter (e.g., the likelihood ratio positive of MRI) is represented by a random variable that is chosen from a probability distribution reflecting the degree of uncertainty for that parameter. We used normal probability distributions to represent the three parameters in the model, each distribution was constrained to avoid illegal values. The probability of breast cancer and likelihood ratio negative of CBE and mammography were bounded between zero and one; the likelihood ratio positive for MRI was bounded as greater than or equal to one. The model was recalculated 5000 times

Table 1. Model parameters*

Parameter	Value	95% confidence interval†
Sensitivity of mammography and CBE	82.2%	
Specificity of mammography and CBE	98.8%	
Likelihood ratio negative of mammography and CBE‡	0.18	0.12-0.24
Sensitivity of MRI	95.6%	
Specificity of MRI	68.6%	
Likelihood ratio positive of MRI§	3.05	2.00-4.11

*CBE = clinical breast examination; MRI = magnetic resonance imaging.

†Confidence intervals are shown only for the likelihood ratios, the parameters used in the study.

‡The likelihood ratio negative is defined as the ratio of one minus sensitivity to specificity.

§The likelihood ratio positive is defined as the ratio of sensitivity to one minus specificity.

for each set of parameters using a Monte Carlo simulation software package (@Risk version 3.0 for Windows; Palisade Corp., Newfield, NY). The 95% CIs for the likelihood ratios are shown in Table 1.

Sensitivity analyses. To test the effects of uncertainty in model parameters on model results, we performed several sensitivity analyses. These analyses involve varying the model parameters over a range of values. We performed sensitivity analyses on the initial prevalence of disease, the sensitivity and specificity of mammography and CBE, and the sensitivity and specificity of MRI. We also examined the effect of assuming that the combined sensitivity of mammography and CBE was lower for younger women than for older women, using an approximate ratio of sensitivity of mammography in younger women to that of older women based on the medical literature (28,50-53).

RESULTS

Meta-analyses

The results of the literature search for the MRI parameters revealed 360 MEDLINE entries identified, of which 14 met eligibility criteria for use in the meta-analysis. After removal of duplicated data, we used 12 studies in the meta-analysis; these studies are summarized in Appendix Table 1. Sensitivity of the studies ranged from 91% to 100%. The studies showed a wide range of specificity, ranging from 37% to 89%.

Parameter estimates for the likelihood ratios used in the analysis are shown in Table 1. The sensitivity and specificity for mammography and CBE and for MRI are included for reader information; the likelihood ratios were used for the model analyses. As can be seen in Table 1, the summary measure of sensitivity of MRI is quite high, but that of specificity is modest. The summary likelihood ratio positive for MRI, 3.05, is reasonably small. In comparison, the likelihood ratio positive of mammography and CBE would be 68.5, due to the very high specificity of the combination of these two tests.

Fig. 2 shows the summary ROC curve for the MRI studies along with the operating points of these studies. The curve shown is a partial ROC curve to avoid extrapolation past the range of available data. While we combined studies using different MRI techniques, no study was an outlier on the regression used to create the curve, suggesting that no study was operating at a sensitivity and specificity significantly different from those combinations on the summary ROC curve.

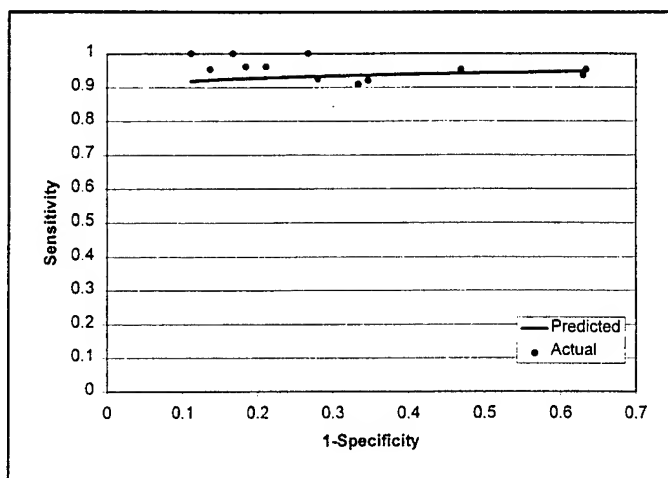


Fig. 2. Summary receiver-operating characteristic curve for magnetic resonance imaging (MRI) of the breast. This curve represents a weighted summary of the studies on the diagnostic accuracy of MRI for the detection of breast cancer.

Simulation Model Results

Table 2 shows the calculated initial prevalence of disease for the overall population, whites, blacks, and women at high risk. These figures represent roughly three times the SEER yearly incidence of disease. Among women having an abnormal mammogram (American College of Radiology categories 4 and 5) (54) and/or CBE who are recommended to have a biopsy procedure, where that biopsy is negative for cancer, the estimated positive predictive values of serendipitous lesions found on MRI are listed in Table 3. For our baseline analysis, the product of the likelihood ratio negative of mammography and CBE and the likelihood ratio positive of MRI is less than one. As a result, the age- and race-specific positive predictive values of MRI for serendipitous lesions are actually smaller than the initial prevalences of cancer shown in Table 2. Positive predictive values range from less than 1% chance of disease up to a high estimate of a 1.9% chance of cancer in an MRI lesion found in an 80-year-old high-risk woman. In general, the positive predictive value of MRI increases with age (Table 3). Older blacks tend to have a lower positive predictive value than older whites (although the CIs overlap), but the positive predictive values for blacks and whites under age 60 years are reasonably similar.

Table 2. Estimated age- and race-specific prevalence of breast cancer*

Age, y	Total, %	White, %	Black, %	High risk, %†
35-39	0.24	0.24	0.25	0.53
40-44	0.40	0.40	0.44	0.84
45-49	0.63	0.64	0.65	1.40
50-54	0.68	0.70	0.60	1.37
55-59	0.79	0.81	0.74	1.58
60-64	0.98	1.03	0.82	1.95
65-69	1.17	1.23	0.98	2.34
70-74	1.42	1.48	1.17	2.85
75-79	1.53	1.58	1.27	3.06
≥80	1.67	1.73	1.30	3.34

*Values expressed as a percentage; 1% would be equivalent to 1000 cancer cases per 100 000 women.

†A high-risk population is defined for this analysis as a population that has twice the age-specific incidence of breast cancer compared with the U.S. total population incidence.

Table 3. Age- and race-specific positive predictive values for cancer (with 95% confidence intervals [CIs]) for women with a serendipitous breast lesion found on MRI and a benign index lesion

Age, y	Predictive value, % (95% CI)			
	Total	White	Black	High risk*
35-39	0.13 (0.07-0.21)	0.13 (0.07-0.20)	0.14 (0.07-0.22)	0.29 (0.16-0.46)
40-44	0.22 (0.12-0.35)	0.22 (0.12-0.35)	0.24 (0.13-0.38)	0.46 (0.25-0.73)
45-49	0.35 (0.19-0.55)	0.35 (0.19-0.55)	0.36 (0.20-0.55)	0.78 (0.43-1.2)
50-54	0.38 (0.21-0.58)	0.39 (0.21-0.60)	0.33 (0.18-0.51)	0.76 (0.42-1.2)
55-59	0.44 (0.24-0.67)	0.45 (0.25-0.68)	0.41 (0.22-0.63)	0.88 (0.48-1.3)
60-64	0.54 (0.30-0.83)	0.57 (0.31-0.88)	0.45 (0.25-0.70)	1.1 (0.59-1.7)
65-69	0.65 (0.34-0.99)	0.68 (0.37-1.1)	0.54 (0.29-0.84)	1.3 (0.71-2.0)
70-74	0.78 (0.44-1.2)	0.82 (0.45-1.3)	0.65 (0.35-0.99)	1.6 (0.88-2.4)
75-79	0.84 (0.46-1.3)	0.87 (0.49-1.3)	0.70 (0.39-1.1)	1.7 (0.94-2.6)
≥80	0.93 (0.51-1.4)	0.96 (0.52-1.5)	0.72 (0.39-1.1)	1.9 (1.0-2.9)

*A high-risk population is defined for this analysis as a population that has twice the age-specific incidence of breast cancer compared with the U.S. total population incidence.

Sensitivity Analyses

Cancer prevalence. The relationship between the initial prevalence of cancer and the positive predictive value of MRI given a negative mammogram and CBE is shown in Fig. 3. Under our baseline conditions of diagnostic accuracy, the positive predictive value of MRI for a serendipitous lesion is less than the starting prevalence of cancer. This finding is explained by the fact that, under our baseline estimates of diagnostic accuracy, the finding of a negative mammogram and CBE lowers the probability of disease more than the finding of a positive MRI raises the probability.

Sensitivity and specificity of MRI. Fig. 4 shows a graph of

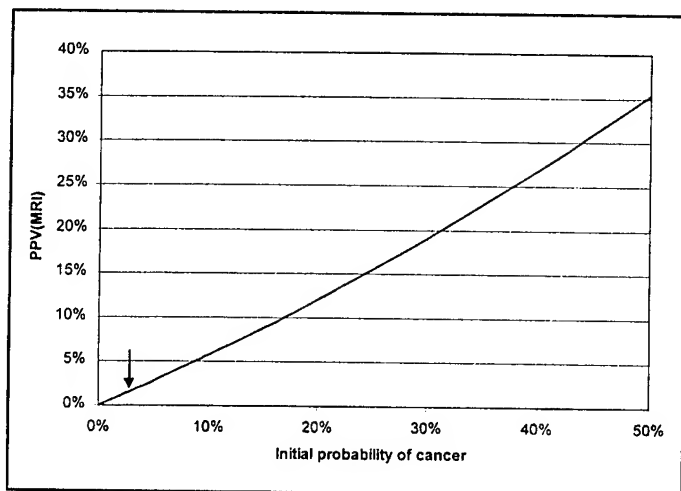


Fig. 3. Sensitivity analysis of the effect of initial prevalence of cancer on the positive predictive value (PPV) of magnetic resonance imaging (MRI), given a negative mammogram and clinical breast examination. The arrow marks the upper bound of the range of initial prevalences of cancer presented in Table 2.

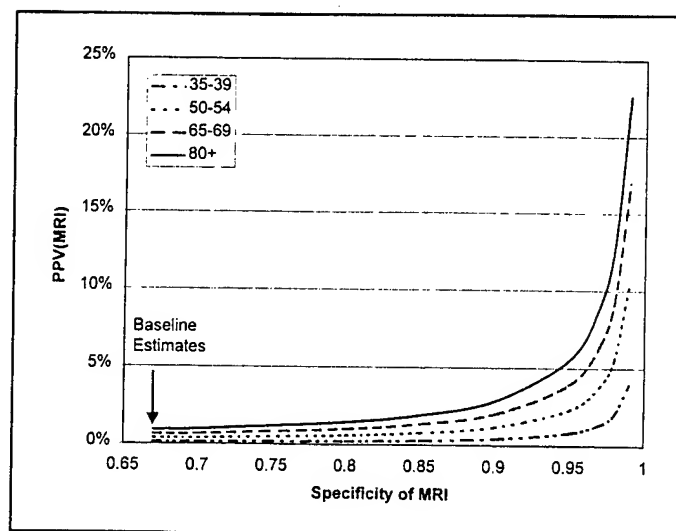


Fig. 4. Sensitivity analysis on the effect of specificity of magnetic resonance imaging (MRI) on the positive predictive value (PPV) of MRI, given a negative mammogram and clinical breast examination. Data are presented for four age groups of women at average population age-specific risk of breast cancer.

the specificity of MRI (for a constant sensitivity) versus the positive predictive value of the MRI, given a negative mammogram and CBE, for selected age groups. For women of all ages, if the specificity of MRI were lower than our baseline estimate, then the positive predictive value of the test would be lower; If the specificity of MRI were to improve, then the positive predictive value of the test would improve. For example, for an average 60-year-old woman to have a 5% chance of cancer with a positive MRI in this setting, the specificity of MRI would have to be more than 95%. For all ages for women at average population risk, the specificity of MRI would need to be at least 94% to raise the positive predictive value to 5%. Improving the sensitivity of MRI will also slightly improve the positive predictive value, but the analysis is not as dependent upon this parameter. We also varied the likelihood ratio positive of MRI across the range of values represented in the summary ROC curve in Fig. 2, bounded by the range of specificities seen in the analyzed studies. If the most specific point on the summary ROC curve is used, the likelihood ratio positive for MRI is 8.3, and the product of the likelihood ratios would be 1.5. Thus, if future use of MRI for a particular finding demonstrated a sensitivity and specificity at this point on the curve (92% and 89%, respectively), the positive MRI could raise the probability of cancer, for example from a pre-test probability of 1.5%–2.3% for a 75-year-old average woman in the population.

Sensitivity and specificity of mammography and CBE.

Fig. 5 shows a graph of the relation between the sensitivity of mammography and the positive predictive value of MRI. If mammography were more sensitive than our baseline estimate of 82%, the positive predictive value of MRI would be lower than estimated. As sensitivity of mammography and CBE decreases, the positive predictive value of the MRI increases, although even with a sensitivity of 40% for mammography and CBE, the positive predictive value of MRI does not reach 5% for average risk women. If the specificity of mammography and

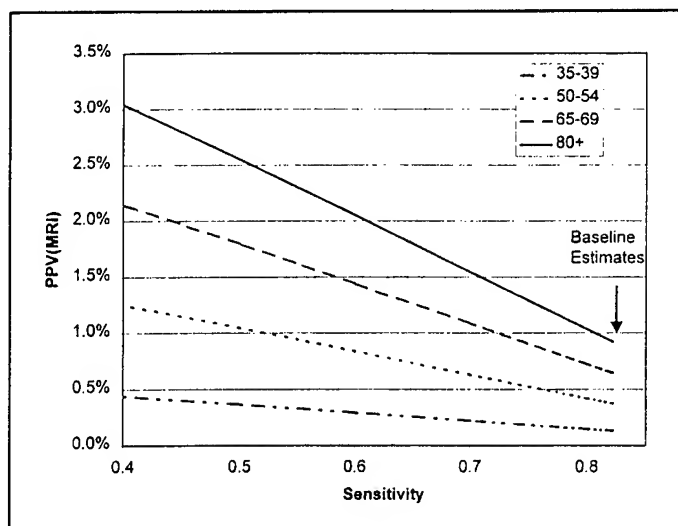


Fig. 5. Sensitivity analysis on the effect of sensitivity of mammography and CBE on the positive predictive value (PPV) of magnetic resonance imaging (MRI). Data are presented for four age groups of women at average population age-specific risk of breast cancer.

CBE decreases, then the positive predictive value will improve, although the analysis is much less dependent on changes in this value. We also examined the effect of our assumption that the sensitivity of mammography and CBE are independent of age. In this sensitivity analysis, we assumed that the combined sensitivity of mammography and CBE for woman younger than 50 years old was 0.8 times our baseline sensitivity. This assumption did not cause large changes; the positive predictive value of MRI ranged from 0.3% for an average 35- to 39-year-old woman to 1.5% for a 45- to 49-year-old high-risk woman. The product of the likelihood ratios for this sensitivity analysis was 1.1; so the combination of negative mammography and CBE did not largely raise the probability of disease for these women whose initial prevalence of disease is small.

DISCUSSION

We know of no other work that focuses on the issue of serendipitous breast lesions in women without known cancer. This work was initiated to help guide clinicians who were faced with decisions of whether or not to pursue serendipitous breast lesions found on MRI.

Our analysis has shown that the positive predictive value for cancer of serendipitous lesions found on MRI is quite low. There are several reasons that MRI has such low positive predictive values. First, the positive predictive value is affected by the probability of disease in the women who undergo the test. Overall, the general population prevalence of cancer is low.

Second, the mammogram and CBE add information to the MRI. The mammogram and CBE are, by definition, negative in the area that the serendipitous lesion was found. The fact that these two tests are negative lower the probability that a woman has cancer from her baseline. Our baseline estimates of the sensitivity and specificity of mammography and CBE suggest that the probability of cancer after these tests are negative is roughly one fifth the initial chance of cancer.

Finally, the lack of specificity of MRI contributes to the low

positive predictive value of this test. For our baseline estimates of diagnostic accuracy, the specificity of MRI would have to be 83% to have a positive predictive value of MRI for a serendipitous lesion equal to the initial prevalence of cancer. While the studies we examined uniformly reported sensitivity more than 90% for MRI, the specificity of MRI ranged from 37% (55,56) to 89% (57). We have found on meta-analysis that the specificity is quite low; however, should future MRI techniques preserve current sensitivity while greatly improving specificity, then the positive predictive value may become high enough to warrant an immediate biopsy procedure for further evaluation. If the sensitivity of future techniques is similar, then the positive predictive values for serendipitous lesions found using these MRI techniques can be approximated by finding the appropriate value for a woman's age and the technique's specificity on the graph in Fig. 4.

Sensitivity analyses show that the probability of cancer in these serendipitous lesions remains extremely low over a wide range of assumptions. As noted above, the analysis was perhaps most dependent on the specificity of MRI, with higher positive predictive values for higher specificity. However, to have the positive predictive value for a 50-year-old woman raised to 5%, for example, the specificity of MRI would have to be 98% given our baseline estimate of sensitivity. Also, the lower the sensitivity of mammography and CBE combined, the better the positive predictive value of MRI; however, the sensitivity of mammography and CBE would have to be 55% for MRI to have a positive predictive value of 1% for 50- to 54-year-old average-risk women.

There are several caveats that should be considered when evaluating our results. First, while our results are based on the best estimates of MRI performance from currently available medical literature, none of the studies specifically address MRI characteristics for incidental lesions. Ideally, future research would include a multicenter, consecutive case series in which all patients with serendipitous lesions and benign index lesions either had an excisional biopsy, an MRI-guided biopsy procedure, or close clinical follow-up to determine the probability of cancer in these serendipitous lesions.

Second, we are currently unable to test the validity of the assumptions underlying this model. However, over a broad range of assumptions, our conclusions that MRI has a very low positive predictive value for serendipitous lesions do not change.

Third, we use a person level analysis, instead of a lesion level analysis. We use this level of analysis to calculate the probability that a woman with a serendipitous finding has cancer, instead of the probability that an individual lesion has cancer. Although we are more interested in the former probability, it is difficult to estimate whether a systematic bias is introduced for women with multiple serendipitous lesions due to lack of data on the risk of cancer with multiple serendipitous lesions compared with a single lesion. If each lesion were statistically independent, then our results, which present data for an average woman with serendipitous lesions, would overestimate the probability of cancer in women with a single serendipitous lesion and underestimate the probability for women with multiple lesions. If the risk of cancer in each of multiple lesions is highly correlated, then the probability of cancer will be similar, regardless of the number of lesions.

Fourth, we are interested in the probability of finding invasive breast cancer in this study; we do not include DCIS in the calculation for positive predictive value. Many women who are diagnosed with DCIS by biopsy do not develop invasive breast cancer (58), although if DCIS is diagnosed then treatment is recommended (59). While the incidence of diagnosed DCIS is currently less than that of invasive cancer (32), an autopsy study (60) suggests that the prevalence of undetected DCIS may be larger than that of undetected invasive cancer. Thus, if DCIS were included, the positive predictive value of MRI would increase over our estimates due to an increase in the pretest probability of having disease, albeit by including lesions of more questionable significance than invasive cancers.

These results apply to women who are "typical members of the population." We include high-risk women, e.g., someone with a strong family history of cancer or with a previous history of a biopsy for benign breast disease. This analysis does not apply to someone for whom there is a very high prior probability of cancer. Excluded from this analysis would be women who have a BRCA1 or BRCA2 breast cancer genetic susceptibility mutation, which put women at much higher lifetime risk of cancer than those with a family history but without a susceptibility mutation (61,62). Also excluded in this analysis are those women who have a high clinical suspicion of having a cancer; for instance, if the serendipitous lesion were found in a woman who is being worked-up for findings suspicious for metastases in other organs or a woman who has known breast cancer or prior

breast cancer, the results of this analysis would not be applicable. Also, this analysis is specific to one point in time. There are currently no data on the positive predictive value of MRI for lesions that change over time. Lesions increasing in size on follow-up MRI, for example, may have a higher probability of being cancer than the one-time finding of a serendipitous lesion modeled here.

Finally, the optimal threshold positive predictive value for cancer for which a biopsy procedure of a suspicious lesion should be performed is not well established. This threshold probability would be dependent on a full evaluation of the risks and benefits of a biopsy procedure, for example, balancing the risks of an invasive procedure versus the consequences of potentially delaying diagnosis of a cancer. We provide the probabilities shown in Table 3 as data to assist clinicians and patients in making decisions about further evaluation of serendipitous MRI lesions. The results of this analysis indicate that the probability that a woman with serendipitous lesions found on MRI has breast cancer is lower than the approximately 15%–35% probability of finding cancer in women currently undergoing a biopsy procedure (3–6). Thus, it is unlikely that an immediate biopsy procedure would be the most beneficial strategy.

In summary, we have found that, in women with a suspicious lesion on mammogram and/or CBE found to be benign, serendipitous breast lesions found on MRI are extremely unlikely to be malignant. While the risk is certainly not zero, for a typical woman the probability of cancer in these lesions is low enough that an immediate biopsy procedure could be avoided.

Appendix Table 1. Summary of magnetic resonance imaging (MRI) studies* used in analysis

Year	Study (reference No.)	Level of analysis†	Sensitivity, %	Specificity, %	No. of patients	Contrast MRI techniques‡			Pre- and post-contrast comparison
						Precontrast	Dynamic imaging	Postcontrast	
1993	Cross et al. (55)	Lesion	95	37	41	RODEO	No	RODEO	No
1993	Harms et al. (56)	Lesion	94	37	30	RODEO	No	RODEO	No
1994	Boetes et al. (63)	Lesion	95	86	83	3D MP-RAGE	Turbo T1 SGE (60)	No	Subtraction
1994	Gilles et al. (64)	Person	95	53	144	T1 spin-echo	T1 spin-echo (6)	T1 spin-echo	Subtraction
1994	Turket et al. (65)	Lesion	100	83	35	T2 spin-echo; T1 spoiled GRASS	T1 spoiled GRASS (8)	3D T1 spoiled GRASS	No
1995	Stomper et al. (66)	Lesion	92	65	49	T1; T2 spin-echo; T1 SPGR	T1 SPGR (10)	No	Subtraction
1996	Heiberg et al. (67)	Lesion	100	73	56	25 patients: T1; T2 31 patients: 3D SPGR	3D SPGR (8)	No	Subtraction
1996	Obdeijn et al. (68)	Person	91	67	54	STIR	2D T1 SGE (3)	STIR	Subtraction
1996	Perman et al. (57)	Lesion	100	89	28	T1 Full Fourier	T1 Full Fourier 3D Dynamic Half Fourier (6)	No	No
1997	Bone et al. (69)	Breast	92	72	220	3D T1 SGE	No	3D T1 SGE	No
1997	Helbich et al. (70)	Lesion	96	82	66	65 patients: T2; 3D T1 SGE 3 patients: T2; Dynamic T1 SGE	65 patients: 3D T1 SGE (6) 3 patients: Dynamic T1 SGE (6)	No	Subtraction
1997	Nunes et al. (71)	Person	96	79	192	T1 spin-echo; T2 spin-echo	67 patients: 2D SPGR 125 patients: 3D SPGR	No	No

*All studies used machines with 1.5 Tesla MRI units except for Helbich's study where a 0.5 Tesla machine was used on three patients. All studies gave doses of gadolinium of 0.1 mg/kg body weight except for Boetes (0.2 mg/kg) and Obdeijn (20 mL for all patients).

†Level of analysis refers to the unit used for calculating sensitivity and specificity.

‡RODEO = rotating delivery of excitation off-resonance; MP-RAGE = magnetization-prepared rapid gradient echo; SGE = spoiled gradient echo; GRASS = gradient-recalled acquisition in the steady state; SPGR = spoiled gradient-recalled echo; STIR = short tau inversion recovery; 2D, 3D = 2 or 3 dimensional. Numbers in parentheses represent the numbers of times images were acquired.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Supported by contract DAMD 17-96-C-6069, "Breast Cancer Support Contract," from the Department of the Army.

Manuscript received March 25, 1998; revised September 22, 1998; accepted September 25, 1998.

EDITORIALS

Serendipitous Breast Lesions on Magnetic Resonance Imaging: Why Is This Lesion Different From All Other Lesions?

Larry Kessler, R. James Brenner

Dr. Gamliel,¹ the local mammographer, refers a patient with a suspicious lesion that he doesn't think is cancer to the local magnetic resonance imaging (MRI) machine for a further test. The result confirms his suspicion: the lesion he had seen on mammography appears benign and there is no apparent worry. However, unexpected news arrived in the report: there is another lesion in the same breast that had not been detected by the initial mammogram. Dr. Gamliel is about to recommend surgical biopsy when his expert colleague says she has just read an article in the *Journal of the National Cancer Institute* about these lesions and the patient need not be sent for any invasive procedures. Astonished, Dr. Gamliel asks his colleague, "Why is this lesion different from all other lesions"? When his colleague has no satisfactory answer, he returns home to ponder the problem.

Dr. Gamliel sat down at dinner faced with the intriguing challenge of the question at hand and immediately recognized that he had four children who could help him formulate an answer. He gave them a copy of the paper by Lawrence et al. (1), published in this issue of the *Journal*, and decided to pose to each of them a single question that would, in part, address the initial question and help develop a more complete answer.

He asked his first-born son, the official at the country's most powerful regulatory agency: "What do the label and promotional claims of the MRI manufacturer say regarding incidental lesions"? (He did not like the label "serendipitous"—it just seemed to have the wrong connotation.)

The regulator addressed the problem thus: When the MRI machine came to us for review and approval, it not only promised a new era in diagnostic imaging but began to fulfill a niche in medical imaging not fully appreciated before the advent of the technology. However, MRI machines are approved only for general diagnostic use—no studies have been submitted to the Food and Drug Administration for any specific indication. Therefore, the manufacturer provides no guidance as to what to do with these findings or what they mean to the clinician. The industry looks to the clinical and public health community to provide research examining the risks and benefits of treating these lesions in order to refine their label, their equipment, and to aid in future development.

Next, Dr. Gamliel turned to his eldest daughter, the statistician, and asked, "Does this decision model give me enough information to confidently reject a recommendation for biopsy"?

The statistician responds: This study has numerous strengths, but some important weaknesses that must be acknowledged in order that we understand its implications. First, there are quite a few assumptions that underlie the composition of the model and its analysis. For example, the assumptions contained in the formula for post-test odds have a dramatic negative effect on the positive predictive value of MRI, and it is this low value that heavily influences the decision model. Other key assumptions include: the sensitivity and specificity of MRI for detection of breast cancer is the same for incidental as for index lesions and that diagnostic accuracy of clinical breast examination (CBE) and mammography is conditionally independent of MRI. The most important strength of this analysis lies in the direction it provides for future research and the identification of key parameters that must be measured in just such a study.

His other daughter is a skilled lawyer, and he poses the very difficult question, "What are my legal and ethical responsibilities in this particular case and in other similar cases"?

The lawyer ponders the problem and reminds her father of how Disraeli dismissed the usefulness of statistics. How can you not follow to completion the detection of an enhanced MRI lesion, however incidental it may be, she asks? It's one thing not to know something is there. But, once you have discovered clear evidence of some irregularity, once you tell the patient as you must ethically and legally, and once the possibility of cancer, even a remote one, has been raised with no other means of surveillance except biopsy or repeat MRI, you must take a serious look at that lesion. With no longitudinal studies to show the feasibility or benefit of "benign neglect," your statistics are not yet strong enough to defeat my claim of negligence based on the risk factors of my particular client. Unless my client is under a clinical protocol with the aim of following these apparently low-risk lesions

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See "Notes" following "References."

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and she is aware of the potential risks and benefits, the legal imperative here suggests that once you have made the referral to MRI you must deal with all the findings, positive or otherwise.

Finally, he turns to his youngest son, an exceptional clinician (a surgeon and radiologist) and asks, "Doesn't this lesion require the identical clinical attention that any other lesion found on MRI would dictate; do I have different clinical or ethical responsibilities in this particular case"?

The doctor appears conflicted about the situation, especially after hearing his siblings. He wants to entrust his patient's care to these statistics, after all he has a degree in public health, but it doesn't appear so simple, especially when he knows that delay in diagnosis of breast cancer is one of the most litigated claims in America. Look, he says, some of these "lesions" are dependent on menstrual cycles, so many represent benign proliferative disease. Yet, a few (admittedly a very few) are cancer, and if it's "my" cancer, it's my problem. The mammographic examination and CBE didn't show it the first time, just like some of those cancers metastatic to lymph nodes that are shown only on MRI. I'm not sure I can follow it with these more conventional tools the second time. Close follow-up, like my stock portfolio, may sound better than it really is. Therefore, the recommendation of the authors, that these lesions need not be subject to im-

mediate biopsy, while likely a reasonable scenario in the future, requires additional clinical study for validation.

Dr. Gamliel reclines in his chair, finishes his fourth cup of wine, and tries to summarize:

Thank you my children, your collective wisdom has persuaded me that we are at a starting point, not an end point. Truly, it is too early to decide the appropriate management of these incidental findings. The protocols have not been standardized, the information not much better than anecdotal, and no longitudinal studies of these lesions are available to establish a reasonable approach from a clinical perspective. Perhaps you will help me write a multicenter grant for the study of these incidental lesions, with a focus on a well-standardized protocol for longitudinal study. May we hope that future serendipity will not throw us such a difficult curve ball.

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NOTE

¹Dr. Gamliel is a fictitious character used to convey the editorial message.

Lest We Abandon Digital Rectal Examination as a Screening Test for Prostate Cancer

Joseph W. Basler, Ian M. Thompson

Until the mid-1980s, early detection for prostate cancer had only one tool—digital rectal examination (DRE). The tool is subjective with high interobserver variability (1,2), upward of 10% of prostates are considered abnormal, but only about 1%–2% of men examined are found to have disease. Even then, two thirds or more of the cancers discovered are found to be pathologically advanced (3). Perhaps more worrisome is the fact that, in one study, many men who ultimately died of prostate cancer had a normal DRE at the time of diagnosis (4).

Enter prostate-specific antigen (PSA) testing. There is no question that PSA testing has improved our ability to detect prostate cancer at an earlier clinical stage. PSA testing has 1) dramatically increased the number of tumors detected, 2) detected a population of tumors [stage T1c (5) that are by most measures clinically important, and 3) streamlined our metastatic evaluation of prostate cancer (e.g., identifying a class of patients for whom bone scans and even lymph node dissections may be unnecessary). By using PSA derivatives such as lower PSA thresholds for biopsy (e.g., 2.5 ng/mL for all men), age- and race-adjusted cutoffs, free/total PSA ratio (<25%), PSA/transition zone volume density, etc., the majority of prostate cancers can probably be detected serologically.

So what do we do with our clinical relic of times past? Do we discard DRE and perform our early diagnosis *en absentia*: merely ask the patient to have a blood test and never examine the patient? Reporting in this issue of the Journal, Schröder et al. (6) would have us believe so. They screened 10 523 men aged 54–76 years with three tests—DRE, measurement of PSA levels, and transrectal ultrasonography (TRUS). Using estimated disease prevalence, they determined the performance characteristics of DRE and PSA. Across the board, the performance of PSA was superior to DRE. However, we are not yet ready to dismiss DRE because of concerns with the study of Schröder et al. and a body of evidence supporting the value of DRE.

We have several criticisms of the methodology used by Schröder et al. (6) that directly affect the stated conclusions. 1)

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[Accepted with Revisions to Cancer Epidemiology, Biomarkers, and Prevention]

**COST OF GENETIC COUNSELING AND TESTING FOR BRCA1 AND BRCA2
BREAST CANCER SUSCEPTIBILITY MUTATIONS**

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Funded by: Contract DAMD 17-96-C-6069, "Breast Cancer Support Contract", from the Department of the Army, and grant number 9 R01 HG01846-04 from the National Human Genome Research Institute.

Running Head: Cost of BRCA1/2 Genetic Counseling and Testing

ABSTRACT

Purpose: Counseling and predictive testing are now available for the recently isolated BRCA1 and BRCA2 breast cancer susceptibility genes. We examined the societal costs of providing this counseling and testing to women at risk of having a breast cancer susceptibility mutation.

Methods: Genetic counselors in a research program prospectively monitored the time necessary to provide counseling and results disclosure. A time-motion study was used to determine time spent on phone calls, preparation, and documentation for counseling. Study participants were surveyed to determine travel time and need for dependent care during counseling. The test cost was calculated using the charge for full BRCA1/2 gene sequencing (Myriad Genetics, Inc.) multiplied by a Medicare-based cost-to-charge ratio.

Results: Counselors spent an average of 4.2 hours providing genetic counseling for women at risk of having a susceptibility mutation. Genetic counseling without testing cost on average \$213, while counseling, testing, and disclosure of results totaled \$2057. A brief physician-based counseling instead of genetic counselor-based counseling would produce only small reductions in total costs. Providing counseling and testing to the study population averages \$8034 per mutation found.

Conclusions: The cost of testing and counseling exceeded \$2000. The counseling portion of the cost comprised only 16% of the total cost, with the remainder representing costs associated with testing; thus, alternatives to full genetic counseling which shorten counseling time are unlikely to have a large impact on the overall cost of counseling and testing. The cost of detecting a mutation within a population of women is highly dependent on the prevalence of the mutation in the population.

INTRODUCTION

Recent advances in molecular genetics have lead to the isolation of the BRCA1 and BRCA2 breast cancer susceptibility genes [1,2]. Mutations in these genes may account for up to 10% of cases of breast cancer [3], and are observed in a significant proportion of families with multiple cases of breast and ovarian cancer [4]. Women who carry a BRCA1 or BRCA2 mutation have an estimated 55% to 85% lifetime risk of breast cancer, and a 15% to 60% risk of ovarian cancer [5-8]. Testing for mutations in these two genes is now available commercially.

Information obtained from genetic testing may enable women to make more informed decisions about their medical management. Women who test positive for a BRCA1 or BRCA2 mutation have several options for cancer screening and cancer risk reduction, although long-term studies demonstrating the efficacy of these strategies in mutation carriers are not yet available. Women could choose intensive surveillance, initiated at an early age, to maximize the chances of detecting a cancer early [9]. Based on recent clinical trial data, tamoxifen [10] or raloxifene [11] may be a consideration for breast cancer chemoprophylaxis, although data about the effects of these drugs in mutation carriers are not yet available. However, a recent study demonstrated that oral contraceptive use reduced the risk of ovarian cancer in women with a BRCA1 or BRCA2 mutation [12]. Women with a mutation may also opt to have a prophylactic mastectomy [13] and/or oophorectomy, to decrease the risk of breast and ovarian cancer, respectively. Several decision analyses [14,15] have suggested that a prophylactic mastectomy may prolong life approximately 3 to 4 years for a 30 year old woman with a BRCA1 susceptibility mutation.

BRCA1/2 genetic testing also has limitations and risks. Those testing positive may face

insurance or employment discrimination [16], and may encounter potentially high medical bills for cancer prophylaxis or surveillance due to their elevated risk of developing cancer. Women testing positive may also have higher levels of distress and anxiety than those testing negative [17]. Psychological distress may lead to avoidance of breast cancer screening [18,19], may interfere with comprehension of personal risk [20], and may impact on treatment or surveillance choices [21]. On the other hand, there may be psychological benefits to testing, especially for those persons in high risk families who test negative [22]. However, these individuals may feel falsely reassured that they will not get cancer [16] and therefore may be less likely to adhere to standard screening guidelines.

Counseling can assist women considering BRCA1/2 testing in making informed decisions about undergoing testing, as well as about possible surveillance and prophylactic options based upon the test result. Information about the probability of having a mutation, the risks and benefits of testing, and potential options if test results are positive is frequently provided by a genetic counselor or other appropriate clinician (such as oncology nurses, oncologists, or geneticists). Pre- and post-test genetic counseling, given its broad and complex nature, is time intensive. The amount of time and level of expertise necessary for adequate counseling, while necessary for informed decision making, would suggest that counseling is expensive; however, the cost of providing this counseling has not been well described. We examined the cost of providing genetic counseling for women at high risk for carrying a BRCA1/2 mutation within the settings of a research study. This study is part of an ongoing project evaluating the costs and outcomes of BRCA1/2 genetic counseling and testing.

Clinicians and women are interested in breast cancer genetic susceptibility testing [23-

25], and use of counseling and testing are translating from research tools into clinical practice. Clinicians have ordered BRCA1/2 testing outside of research settings [26], and some managed care organizations are covering part or all of the costs of these genetic tests [27]. As counseling and testing become more common, it is important to better understand the costs involved in providing counseling and testing, and how these health care costs may be impacted as BRCA1/2 counseling and testing continues to translate from research to clinical settings. To better understand these costs, we had three goals for this study. First, we examined the cost of counseling and testing in a research program. Second, we used sensitivity analysis to examine the costs of a hypothetical alternative program of providing physician counseling and testing; a practice which may occur more frequently as BRCA1/2 testing translates to clinical practice. Finally, we use these costs to calculate the cost necessary to find a mutation by testing women from different populations.

METHODS

Study Population

Eligible subjects included women and men enrolled in the Cancer Assessment and Risk Evaluation (CARE) program, a prospective cohort study of BRCA1/2 testing. All study procedures were approved by the Georgetown University Institutional Review Board. Eligible participants had at least a 10% prior probability of carrying a mutation in either BRCA1 or BRCA2, consistent with published recommendations [28]. Participants were identified through both physician referrals and self referrals. After determining eligibility, participants completed a baseline telephone interview to collect data on family history, medical history, risk factors, and

psychological well-being. After providing written informed consent, individuals participated in a pre-test counseling session (see below). Those opting for genetic testing provided a blood sample for mutation analyses, and results were disclosed during a subsequent genetic counseling session. Probands, the first individuals in a family to be offered testing, were women with a diagnosis of breast cancer (or in rare instances, men with a diagnosis of breast cancer) or ovarian cancer, often at a young age and in conjunction with a family history of these diseases. If a mutation was identified in the family, then male and female relatives were invited to participate in the program. All genetic counseling and testing was offered free of charge to the participants. Follow-up interviews to assess the outcomes of testing are completed at 1, 6, and 12 months after testing (or declining test results). The present study focuses on data collected at the pre-test interview and counseling visits.

Genetic Counseling Procedures and Content

The majority of participants in the CARE program completed genetic counseling visits with one of two board-eligible or board-certified masters-level genetic counselors; several were counseled by an oncology nurse with training in cancer genetics. Pre- and post-test genetic counseling was a required part of the study for those interested in testing. Individual disclosure sessions were performed with one of the genetic counselors, and in some cases, a medical oncologist. Regardless of the test result, the genetic counselor contacted the participant about two weeks after the result was given for an unstructured clinical follow-up telephone call.

The content of the genetic counseling sessions was standardized but not scripted for each participant. The following topics were addressed in the pre-test genetic counseling sessions: (1)

a detailed review of the consultand's medical and family history, including compilation of a multi generation pedigree; (2) an overview of hereditary breast cancer and approach to risk assessment; (3) cancer risks associated with BRCA1 and BRCA2 mutations; (3) autosomal dominant inheritance and implications for relatives according to the pedigree; (4) options for medical management including surveillance and risk reduction; (5) the potential benefits, risks, and limitations of testing, including provisions for confidentiality; and (6) an exploration of the patient's anticipated response to test results and coping skills, plans for communication of test results, and resources for support. The post-test session included a review of pertinent material from the first session, with a more tailored discussion of cancer risks, medical management options, risks to relatives, and coping strategies. Supportive counseling was provided as needed.

Measures

Data collected for the present analysis included time costs for counselors to provide counseling and costs for participants to receive counseling. The time necessary for a counselor to counsel a patient was derived from two sources. First, face-to-face counseling time was determined by prospectively recording the counseling time for a sample of 191 patients. Time data were recorded using a categorical scale (< 1 hour, 1-1.5 hours, > 1.5-2 hours, > 2-2.5 hours, > 2.5 hours). The midpoint of each category was used to estimate the time for each patient; the highest category was assumed to have a time of 2.5 hours. Second, counselors' telephone follow-up time and documentation time for counseling and phone calls were determined by monitoring the counselors' activities during a 3 week period. Activities tracked included the time required to provide in-person pre-test genetic counseling, disclosure of test results,

telephone follow-up, in addition to the time spent preparing for the counseling session, and in documenting patient interactions, including genetic counseling summary notes for the chart and the patient. The program counseled both probands and relatives of probands who had known mutations. We based the counselor time costs on that of counseling probands; thus the cost of counseling that we calculate assumes no prior knowledge of mutations in the participant's family.

The time that participants spent traveling to the study site was determined by a written survey administered to 186 women in the study. Time was recorded in categories of <10 minutes, 10-29 minutes, 30-59 minutes, 1-2 hours., >2 hours. Category midpoints were used as the estimated travel time. Participants were asked to specify a time if the highest category was chosen; this value was used if specified, and 2 hours was used if the value was not specified. The survey also asked participants whether they needed child or adult dependent care during the time that they were in counseling.

Data Analysis

To determine the resources necessary for providing genetic counseling and testing, we calculated the average national costs as opposed to the charges for providing these services. Costs considered in this analysis include: personnel costs, non-personnel related costs involved in providing counseling and testing, and patient costs of receiving counseling. We divided costs into two categories: those associated with genetic counseling, and the additional costs associated with genetic testing and disclosure of results. All costs are presented in 1998 dollars.

Personnel costs included the costs of the counselor's time and the time of clerical or

receptionist staff. The time spent by the counselor in preparation, documentation, and telephone follow-up was estimated by determining the ratio of these times to time spent in face-to-face counseling, and then multiplying the face-to-face counseling time by these ratios. Cost of the counselor's time for one patient was determined by multiplying the total number of hours for face-to-face counseling, preparation, documentation, and phone calls spent by the counselor by the average hourly wage plus fringe benefit cost for genetic counselors, as determined by a national survey of genetic counselors [29,30]. This survey of 816 genetic counselors was conducted in May, 1998. We estimated an hourly wage and fringe rate based upon average salary in the U.S., and assuming that the annual salary and fringe total was based upon 2,000 working hours per year.

The cost of clerical time was determined by estimate of the counselors, including time to assemble patient materials, type appointment letters, and review materials returned by patients for completeness. This time was multiplied by an average hourly cost based upon the median weekly earnings for clerical personnel [31]. Counselors' office space necessary for counseling was calculated using the cost to the institution of the counselors' office space, pro-rated for the time spent providing counseling services to one consultand.

We considered two main costs for the patient in receiving counseling: the costs of the time in counseling, including the travel time to reach the counselor's office, and the costs of providing short-term dependent care (if any) while the patient was at counseling. Time costs were determined using the average sex and age-specific hourly wage rates provided by the Bureau of Labor Statistics [32] for an employed woman of the average age of the cohort multiplied by the average counseling and travel times for the participants. Dependent care costs

were estimated for those women reporting needing this care by taking the time necessary to receive counseling multiplied by an estimate of \$8 per hour.

Costs of testing and disclosure were calculated as follows. Personnel costs to provide testing and disclosure include the cost of the genetic counselor's time to disclose the results to the woman and the cost of a phlebotomist's time to draw blood for genetic testing. While a medical oncologist had previously been present with the counselor for disclosure of results to those who tested positive for a mutation, the program's current practice is to have the counselor alone provide disclosure; thus, personnel costs included the counselor's time but not an oncologist's time. Phlebotomists were asked to estimate the time necessary to draw blood for genetic testing; this time was multiplied by the average salary plus fringe benefit cost for a phlebotomist at our institution. Participant costs were calculated in a similar fashion to those for the genetic counseling.

Non-personnel costs of testing included cost to the institution of phlebotomy materials and the cost of the test itself. The cost of testing is based upon the cost of providing full gene sequencing for BRCA1 and BRCA2; the cost of this test is estimated using the retail charge for commercially available full gene sequencing (Myriad Genetics, Inc., Salt Lake City, Utah) using an a cost-to-charge ratio of 0.664:1, representing the ratio for medical care based upon the 1995 Medicare Cost Reports.

We performed two sensitivity analyses to examine changes in our assumptions about the costs involved in counseling and testing. First, since the cost of testing is estimated from a retail charge, we examined the effects of varying the charge-to-cost ratio used to calculate the cost. Second, to examine the effects of physician counseling instead of genetic counselor-based

counseling, we used an estimated physician salary of \$150,000 per year, plus a 23% fringe benefit rate, to calculate a representative hourly time cost for physician counseling. The cost of physician-based counseling and testing was then calculated as a function of the time spent by physicians compared to genetic counselors.

To examine the costs of screening in different populations, we estimated the cost of counseling and testing that would be necessary on average to find one BRCA1 or BRCA2 mutation in these populations. To perform this analysis, we first calculated the number needed to test to find a mutation, defined as the inverse of the prevalence of the mutations in the population of interest. We assumed that counseling and testing would consist of full pre-test counseling as represented by the proband counseling in CARE, and that full gene sequencing followed by post-test counseling. Thus, the cost of finding a mutation is calculated by:

$$Cost = \frac{[Cost_{Counseling} + Cost_{Disclosure, Testing}]}{prevalence}.$$

Testing in some populations may not require full gene sequencing as the initial test. For example, approximately 90% of Ashkenazi Jews who had a BRCA1 or BRCA2 mutation were found in one study to have one of three founder mutations: 185delAG or 5382insC in BRCA1, or 6174delT in BRCA2 [4]. In this group we examine the cost per mutation found for two testing strategies: (1) test all women for the three founder mutations, and stop if this test is negative; and (2) test all women for the three founder mutations, and if the test is negative then proceed to full gene sequencing. The cost per mutation found for the first strategy was calculated using the charge for testing for these 3 founder mutations multiplied by the cost-to-charge ratio substituted

for the cost of full gene sequencing in the following equation:

$$Cost_{founder} = \frac{[Cost_{Counseling} + Cost_{Disclosure, founder\ testing}]}{prevalence * sensitivity_{founder\ testing}},$$

where the sensitivity of the founder mutation testing is estimated at 0.9 [4]. Cost per mutation found for the second strategy was calculated with the following equation:

$$Cost_{founder} = \frac{[Cost_{Counseling} + Cost_{Disclosure, founder\ testing}] + [(1 - prevalence * sensitivity_{founder\ testing}) * Cost_{sequencing}]}{prevalence}.$$

In this scenario, all participants receive the cost of founder mutation testing, and those testing negative (represented by the 1-prevalence*sensitivity term above) also receive the cost of full gene sequencing. We assume that all women would receive only one pre-test counseling session and one post-test disclosure.

RESULTS

Cohort Characteristics

Participants in the program had an average age of 47.3 years (s.d. 12.2); the majority (71%) of the cohort had completed college. Of the 181 participants for whom data on time of counseling are available, 127 (70.2%) were affected either by breast or by ovarian cancer. One

hundred twenty three participants (68.0%) were probands, and 58 were relatives of probands with known mutations. There were 161 women and 20 men in the study; only 3 of the males were probands. Genetic test results were available for 159 of these participants; 38 (23.9%) tested positive for a known deleterious BRCA1 or BRCA2 mutation.

Counseling Costs

Figure 1 shows the distribution of counseling times for the cohort by cancer status. On average, the counselors spent 1.63 hours (s.d. 0.40) of time in face-to-face counseling for each proband in the study, significantly longer than the average 1.33 hours (s.d. 0.43) spent counseling relatives ($p < 0.0001$ by two-tailed t-test). For this time spent with a proband, the counselors spent approximately 0.46 hours in phone conversations with the participant, and another 2.13 hours preparing for and documenting the counseling, for a total time of 4.2 hours spent by the counselor in order to provide counseling for 1 participant. Costs of counselor time were calculated using a national average of salary plus fringe benefits of \$53,755 per year, or an average hourly rate of \$26.88 per hour. Using this rate, we calculate a total cost of counselors' time of \$119 per proband (Table 1).

The costs of clerical time and participant time are shown in Table 2. These costs are based upon an estimate of 30 minutes of clerical time necessary for each proband counseled, and of an average of 5.51 time spent by participants undergoing counseling. An average of 14% of participants need a care-giver for a child or dependent adult during the counseling session. Non-personnel costs for counseling include the office space for the counseling session.

Testing Costs

The additional costs associated with receiving testing in addition to counseling are also listed in Table 1. Costs include the costs of the phlebotomist's time, estimated by our phlebotomists at 30 minutes average per person. This estimate encompassed time to complete test requisition forms and delivery of samples. For patients who opted to obtain their test results, an additional 0.61 hours (s.d. 0.29) of face-to-face counseling, on average, was required to disclose the result to the participant. The major cost of testing is the gene sequencing itself, representing 84% of total costs. Cost associated with the pre-test counseling and post-test disclosure comprised the remaining 16% of the costs.

Sensitivity Analyses

Charge-to-Cost Ratio

Our baseline analysis assumes the charge of \$2580 and a cost-to-charge ratio of 0.664:1. If the cost-to-charge ratio is smaller, representing a greater difference between the charge for the test and the cost of the test, then the cost of the test will be lower. If the charge-to-cost ratio is 0.5:1, then the cost of the test will be \$1290, and the total cost of counseling and testing will be \$1634, with the cost of the test comprising 79% of the total cost.

Physician Counseling

Our analysis examines the cost of having genetic counselors provide counseling and disclosure of results. What would happen to the cost of counseling and testing if physicians

provided this counseling and disclosure instead of counselors? Table 2 shows the impact on costs of physicians providing counseling, as a function of the time spent to provide face-to-face counseling, expressed as a percentage of the time spent by the genetic counselors in this study. Physician counseling, even if much shorter than counseling by a genetic counselor, does not have a large impact on total cost; even if the physician counseling time is 3 minutes, the total cost of testing and counseling are reduced only 9.4% below the baseline cost. If a physician spends time counseling in addition to the counselors, then the overall costs of counseling and testing will increase. For example, if a physician counseled each patient for 10 minutes during the pretest counseling session and the posttest disclosure, then the overall costs would increase by 1.5%.

Cost of Finding a Mutation

Table 3 shows the average cost of counseling and testing needed to be performed to detect one susceptibility mutation in various populations; we assume for this analysis that the people tested do not have relatives with known mutations, so the cost is based upon the cost incurred for probands. The first four entries in Table 3 reflect women without specific founder mutations, so we base testing costs on full gene sequencing. In our research setting of counseling high risk participants, the prevalence of a deleterious BRCA1 or BRCA2 mutation is 26%; therefore, on average, 4 participants need to be tested to find one mutation. At the other extreme, given the low prevalence of the mutation in otherwise unselected women in the general US population, 714 women would need to be tested on average to find a single mutation. Using our estimate of the cost of counseling and testing, the average cost of finding a mutation would be about \$8000 for the high-prevalence CARE sample, but testing unselected women in the US

population would cost approximately \$1.5 million to detect a mutation (Table 3).

If the population tested were Ashkenazi Jewish women, otherwise unselected for cancer history, the cost of testing for founder mutations would be approximately \$23,000 per mutation found (Table 3); however this testing will only detect about 90% of the mutations in the population. If testing for founder mutations detected greater than 90% of mutations, then the cost per mutation found would decrease slightly (to a minimum of \$21,022 per mutation found if 100% of mutations were detected). To detect the other 10% of mutations, using full gene sequencing as a confirmatory test for those testing negative for founder mutations would increase the cost to over \$80,000 per mutation found. Other intermediate strategies could be used for testing Ashkenazi Jewish women, for example testing all women for founder mutations, and for those women who have a first-degree relative (FDR) with breast cancer who test negative, use full gene sequencing as a confirmatory test. Under the assumption that Ashkenazi Jewish women have the same risk of having a FDR with breast cancer as women in the general population, and that the relative risk of having a BRCA1/2 mutation for women translates is equivalent to the relative risk of developing breast cancer for women with an affected FDR [33,34], then this strategy would detect approximately 91.4% of mutations for a cost per mutation detected of \$27,670.

DISCUSSION

There are potential benefits to testing individuals at high-risk for carrying a BRCA1 or BRCA2 mutation. However, there are also substantial costs associated with this testing,

exceeding \$2000 for the combination of genetic counseling and testing. The major expense for this combination is the genetic test itself, for which we used the estimated cost of full gene sequencing. Currently, there are over 400 known or suspected deleterious mutations identified for the BRCA1 and BRCA2 genes [35]. Many families harbor "private" mutations that have never been reported before, but which are known to be deleterious. Full gene sequencing is considered to be the most sensitive method of detecting these mutations [36]. However, in certain populations, a few founder mutations appear to account for the majority of detectable alterations in BRCA1 and/or BRCA2. For example, common founder mutations have been reported in individuals of Ashkenazi Jewish [8], Icelandic [37], or French Canadian [38] descent. Less expensive tests to detect these mutations are available. In addition, in most instances, relatives of an individual with a documented mutation can be tested only for the mutation found in their family. Judicious use of such tests may reduce the overall cost of testing. Also, if testing became more common, economies of scale may reduce the cost of full gene sequencing, eg. by allowing the tests to be run in larger batches decreasing the labor cost for each test in the batch.

The pre-test genetic counseling session represented only 10% of the total cost of counseling and testing. While counseling is a time-intensive procedure, requiring a total of 4.3 hours of the counselor's time, the cost of providing this counseling is small in relation to the cost of the test. Genetic counseling should be considered as part of the informed consent process, and helps to ensure that individuals make knowledgeable choices about testing. This process maximizes the likelihood that individuals will derive some benefits from testing, while minimizing the chances of adverse or unanticipated effects. Moreover, the potential to

misinterpret test results exists [39] and could have substantial implications for patients and families. Women may prefer obtaining pretest counseling with a genetic counselor over either an oncologist or primary care physician, particularly if they desire to discuss psychosocial issues [40]. Given the time intensive and complex nature of such counseling, it is unlikely that offering such services will be feasible for most physicians; most likely making a referral necessary. We have found in this study that physician counseling, even if the counseling provided is much more brief than that provided by a counselor, would not largely impact on the overall cost of counseling and testing. The cost of the test is the largest part of the total cost of counseling and testing, representing 84% of the total, so physician counseling would not result in a large reduction in costs even if much less time was spent by the physicians than by the counselors. In consideration of these findings, we strongly advocate that genetic testing be performed only in conjunction with genetic counseling, performed by a genetic counselor or other specialized provider, consistent with other published recommendations [28,41].

The average cost of finding a mutation in the population depends on the prevalence of the mutations in the populations. The values in Table 3 represent a large range of costs for finding a mutation; this large range is a consequence of the prevalence in the denominator of the equation to determine the average cost to find a mutation. As the prevalence approaches 0, the cost of finding a single mutation approaches infinity. While this study only examines costs, not effectiveness, it is unlikely that unselected counseling and testing of women in the general population will be cost-effective, since the cost of finding a mutation is so high that it is very unlikely that the benefit produced will justify the cost of counseling and testing. Testing unselected women with breast cancer would cost almost \$80,000 per mutation found. Whether

testing these women with breast cancer would be cost-effective would depend on the amount of benefit gained by those in whom a mutation is detected.

Testing Ashkenazi Jewish women for 3 founder mutations is significantly less expensive per mutation found than testing women in the general population with full gene sequencing, due to the ability to use a much less expensive test which will detect a majority of mutations, and a higher prevalence of mutations in the Ashkenazi population. Testing for founder mutations only will miss about 10% of women in the population who have deleterious mutations, however. Whether the increased expense of using full gene sequencing to detect the remaining 10% of mutations is justified by an improvement in outcomes will need further study.

Several caveats should be considered when evaluating our results. First, the costs calculated in this study are the costs associated with a research program, and not those of standard clinical practice. Although BRCA1 and BRCA2 gene testing is still used as a research tool, the use of testing and counseling is also translating into routine clinical practice. As providing testing is a major portion of the costs, we do not expect the overall costs of counseling plus testing to change significantly in clinical practice unless the type of test used were to change. In this study, we are interested in examining the resource utilization (as measured by health care dollars) necessary to provide counseling and testing, thus we use costs of the services in this analysis rather than charges for the providing the services. Retail charges for testing and counseling services will be larger than the costs reported in this study. We have used expert opinion to estimate time costs for ancillary personnel, including secretarial and phlebotomist time, but any misestimation is unlikely to significantly influence the results since the total of these costs represents less than one percent of the cost of counseling and testing. Our value used

for the cost of full gene sequencing is an estimate based upon the model of using commercial testing. The cost of producing a product in private industry is generally not a matter of public record, so we are unable to provide an exact accounting of this cost. To estimate, we use an approximate governmental cost-to-charge ratio. The estimate is similar to an accounted cost of full gene sequencing of the COL2A1 gene [42].

Second, our study evaluated counseling at only one location; content and delivery of counseling may differ at other locations, resulting in differing costs. While the content of genetic counseling for hereditary breast cancer is likely to have similar components in a clinical setting [29], the risk level of the patient, sociodemographic factors such as education level, and protocols of individual centers may vary. For example, some centers have designed their clinics such that patients are seen by a multi disciplinary team including medical oncologists, genetic counselors, nurses, and psychologists [43-45]. In some cases, group sessions may be conducted for pretest education [22]; however, disclosure of test results should take place on an individual basis. Finally, while we considered the costs of the counseling and testing, the benefits are not fully described. Thus, while we can describe the costs of counseling and testing, we cannot estimate the changes in health outcomes such as survival or health-related quality of life due to counseling and testing in this analysis. Decision models would suggest that in those with a BRCA1/2 mutation prophylactic surgery may be beneficial [14,15,46,47], and that testing some high-risk women will improve their outcomes if they make decisions about prophylactic surgery based upon their test result [47].

In conclusion, genetic counseling and testing are associated with significant costs. If testing is considered, detailed accounting of the risks and benefits should be provided to the

consultand; this counseling can be performed for a fraction of the cost of the test itself. Whether the costs of counseling and testing of women at risk for a mutation is justified by the benefits of these interventions has yet to be determined, and will be the subject of future work.

Acknowledgments:

We gratefully acknowledge the contributions of Tiffani DeMarco, MS and Barbara Brogan, RN, MS, for their work with patients in the CARE program, and to David Main, MS, and Carol Kavanagh, MA for statistical and programming assistance. We would also like to thank the participants of the CARE program.

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Table 1. Costs of Genetic Counseling and Testing for Probands

Category	Cost
<i>Counseling Costs</i>	
Counselor costs	\$119
Ancillary personnel costs	\$7
Participant costs	\$80
Non-personnel costs	<u>\$7</u>
Total Counseling Costs	\$213
<i>Testing and Results Disclosure Costs</i>	
Counselor disclosure costs	\$44
Participant costs	\$72
Phlebotomist cost	\$7
Phlebotomy material, office space	\$8
Gene Sequencing	<u>\$1713</u>
Total Testing and Disclosure Costs	\$1844
Total Counseling + Testing Costs	\$2057

Table 2. Cost for Physician-Based Counseling and Testing

Time Spent Counseling	% Time of Counselor*	Cost	% Reduction of Cost†
41 min	25%	\$1996	3.0%
16 min.	10%	\$1909	7.2%
3 min	2%	\$1863	9.4%
20 min. additional**	14.9%	\$2087	(1.5%)

* Compared to 1.63 hr., average time for a genetic counselor to counsel a proband.

† Reduction in cost compared to baseline analysis.

** Assumes 10 minutes time spent by physician at pretest counseling and at post-test disclosure in addition to the baseline amount of counselor time.

Table 3. Cost of Detecting a BRCA1 or BRCA2 Mutation

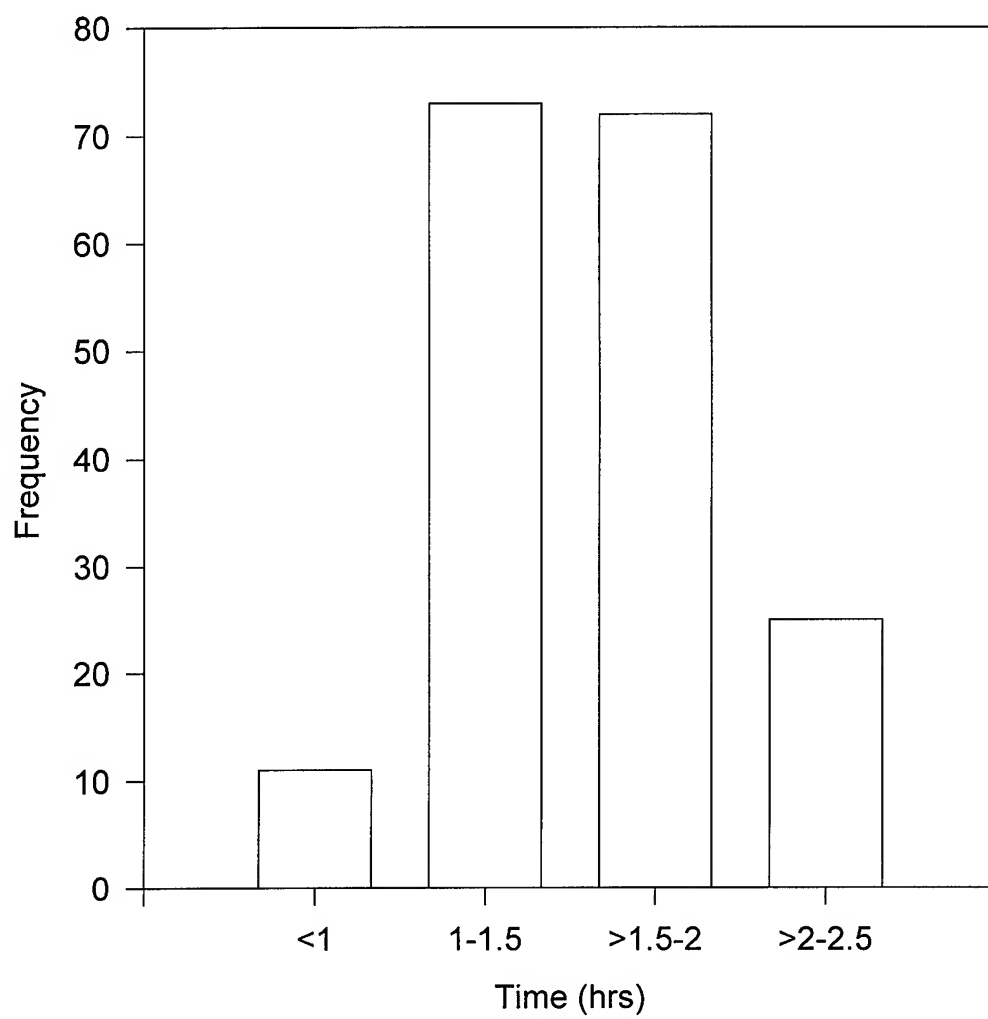
Population	Mutation Prevalence	Reference	Cost to Detect Mutation
CARE*	25.6%		\$8,034
Breast Cancer 21-44 y.o.*	7.2%	[48]	\$28,565
Breast Cancer, unselected*	2.6%	[49]	\$79,104
U.S. Population*	0.14%	[50]	\$1,469,080
Ashkenazi Jews (founder mutations only) [†]	2.4%	[51]	\$23,357
Ashkenazi Jews (founder mutations + full gene sequencing) [‡]	2.4%	[51]	\$82,002

* Average cost of testing and counseling for women in the population of interest necessary on average to have one positive test for a BRCA1 or a BRCA2 mutation, assuming the use of full gene sequencing, and that the test is the gold standard diagnosis of a mutation.

[†] Assuming testing for 3 founder mutations (185delAG, 5382insC, 6174delT), with no further evaluation if the tests are negative.

[‡] Assuming testing for 3 founder mutations (185delAG, 5382insC, 6174delT), and testing those who test negative with full gene sequencing.

Figure 1. Distribution of time taken to provide face-to-face genetic counseling to women at risk for carrying a BRCA1/2 breast cancer susceptibility mutation.



**COST-EFFECTIVENESS OF GENETIC COUNSELING AND TESTING FOR BRCA1
AND BRCA2 BREAST CANCER SUSCEPTIBILITY MUTATIONS
FOR HIGH-RISK WOMEN**

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Funding: This work was funded by Contract DAMD 17-96-C-6069, "Breast Cancer Support
Contract", by the Department of the Army

ABSTRACT

Background: Women with BRCA1 or BRCA2 breast cancer susceptibility mutations are at substantially increased risk of developing breast and/or ovarian cancers. While options are available to manage this cancer risk, the costs and benefits of testing women who are at high risk of carrying a mutation are not well described.

Purpose: To calculate the cost-effectiveness of providing genetic counseling with or without genetic testing for women at high-risk of carrying a susceptibility mutation compared to routine care.

Methods: A computer simulation model was constructed to model the natural history of the development of breast and ovarian cancer in women with and without susceptibility mutations. This model was used to determine the costs and outcomes of three strategies: 1) routine medical care, 2) providing genetic counseling, and 3) providing counseling and genetic testing for BRCA1/2 susceptibility mutations.

Results: For a 45 year old woman at high risk of mutation (15.5% risk of BRCA1, 6.7% risk of BRCA2), the incremental cost-effectiveness ratio of counseling and counseling plus testing compared to routine care were \$85,673/LY and \$42,717/LY, respectively. Increasing prevalence of mutations, earlier age at testing, and greater likelihood of choosing prophylactic surgery would result in improved cost-effectiveness of counseling and testing.

Conclusions: Providing genetic counseling and testing is a cost-effective intervention for women at high-risk of carrying a mutation; however the costs and outcomes are dependent on what options women choose to manage their cancer risk. As risk of carrying a mutation lessens, providing counseling and testing become much less cost-effective.

INTRODUCTION

Recent advances in molecular genetics have lead to the isolation of the BRCA1 and BRCA2 breast cancer susceptibility genes (Miki, et al., 1994; Wooster, et al., 1995). Mutations in these genes may account for up to 10% of cases of breast cancer (Claus, et al., 1996), and are observed in a significant proportion of families with multiple cases of breast and ovarian cancer (Frank, et al., 1998). Women who carry a BRCA1 or BRCA2 mutation have an estimated 55% to 85% lifetime risk of breast cancer, and a 15% to 60% risk of ovarian cancer (Easton, 1995; Ford, 1998; Ford 1994). Testing for mutations in these two genes is now available commercially, and is starting to be used in clinical practice (Cho, 1999). Some insurers now cover part or all of the cost of counseling and testing for breast cancer genetic susceptibility in high-risk women.

Information obtained from genetic testing may enable women to make more informed decisions about their medical management. Women who test positive for a BRCA1 or BRCA2 mutation have several options for cancer screening and cancer risk reduction, although long-term studies demonstrating efficacy of these strategies in mutation carriers are not yet available. Women could choose intensive surveillance, initiated at an early age, to maximize the chances of detecting cancer early (Burke, 1997). Based on recent clinical trial data, tamoxifen (Fisher, 1998) or raloxifene (Cummings, 1999) may be a consideration for breast cancer chemoprophylaxis, although data about the effects of these drugs in mutation carriers are not yet available. Women with a mutation may also opt to have a prophylactic mastectomy (Hartmann, 1999) and/or oophorectomy, to decrease the risk of breast and ovarian cancer, respectively. Decision analyses (Schrag, 1997; Grann 1997) have suggested that a prophylactic mastectomy

may prolong life approximately 3 to 4 years for a 30 year old woman with a BRCA1 susceptibility mutation.

While BRCA1 and BRCA2 susceptibility testing are accepted as a research tool, clinical trials have yet to be performed to test whether genetic counseling and testing reduce morbidity or mortality from breast and ovarian cancer in high-risk women. In this study, we use decision analytic methods to estimate the costs and outcomes of such counseling and testing based upon available data. The simulation model created in this study is used to examine the cost-effectiveness of BRCA1/2 genetic counseling and testing in women who are at high risk of carrying a mutation.

METHODS

We created a computer simulation model to calculate the costs and outcomes of offering genetic counseling and BRCA1/2 testing to women at risk of carrying a susceptibility mutation in one of these genes, compared to offering counseling only, and to routine medical care. The model was programmed using the Visual C++ programming language (Microsoft, Inc., Redmond, WA).

The model was used for a cost-utility analysis. The results are presented in incremental cost-effectiveness ratios, with costs expressed in dollars and effects expressed as quality-adjusted life years (QALYs). We used a societal perspective in this analysis. Our baseline case for this analysis is a 45 year old woman without detected cancer who is at high risk for carrying a BRCA1/2 susceptibility mutation.

The simulation model used a Monte Carlo stochastic simulation technique (Doubilet, et al., 1985) to test the cost-effectiveness of providing counseling and testing for longitudinal

cohorts of women. This simulation technique allows us not only to calculate point estimates for costs and effects, but also to calculate confidence areas for the outcomes. For each counseling and testing alternative, 500,000 individuals were simulated, and the costs and outcomes averaged across the simulation cohorts.

Model Structure

The decision tree diagram representing the initial counseling and testing decision is shown in Figure 1. A simulated cohort of women undergo each counseling and testing alternative: counseling and testing, counseling only, and routine medical care (no counseling or testing). Each woman in the cohort may carry a BRCA1 or a BRCA2 susceptibility mutation, with a probability equal to the prevalence of the mutations in the cohort. For those women undergoing counseling and testing, the test result may be positive for a BRCA1 susceptibility mutation, positive for a BRCA2 susceptibility mutation, or negative for a susceptibility mutation. We assume for our baseline analysis that full gene sequencing of both BRCA1 and BRCA2 genes is performed. We also assume that women will not have both mutations simultaneously. Indeterminate results from full sequencing are considered to be negative in our baseline analysis. The test result may be a true positive, true negative, false positive, or false negative test based upon whether or not the woman is carrying a mutation, and the sensitivity and specificity of the gene tests.

If a woman tests positive for a BRCA1 or BRCA2 mutation, then prophylactic and surveillance options shown in Figure 1 are chosen. The probability of choosing a particular option is based upon the choices of a cohort of women who have tested positive for BRCA1/2 mutations (Lerman, et al., 1997). At the time of data collection, breast cancer chemoprophylaxis with tamoxifen or raloxifene was not a widely available management choice, so we assumed that

10% of the current cohort would choose chemoprophylaxis upon testing positive if this option were available, and that these 10% of women would be women who otherwise would not have chosen surgical prophylaxis. This assumption was subjected to sensitivity analysis.

The prophylactic options chosen affect the probability of developing breast or ovarian cancer; screening options affect the probability of detecting disease once it has developed. Disease development was modeled using a disease initiation Markov model (Beck and Pauker, 1983). Figure 2 shows the longitudinal model of disease development. In this model, the probability of developing breast and/or ovarian cancer in any particular year is a function of the simulated woman's age and BRCA1/2 status; this probability is further modified by any prophylactic procedures chosen. This model also accounts for competing (non-cancer) mortality. We assumed that the probability of developing ovarian cancer was independent of the development of breast cancer, and vice-versa, due to lack of evidence to the contrary. We also assume that all ovarian cancer starts as localized disease; breast cancer can start either as localized invasive disease, or can start as ductal carcinoma in situ (DCIS) and potentially progress to invasive disease.

Once a cancer develops, the disease may be detected either due to screening or due to clinical surfacing. If either cancer is not detected in a particular year, then the disease has a probability of progression to a more advanced stage. Once a cancer is detected, the disease is treated, which incurs a cost of treatment, and a loss in quality of life due to being diagnosed with and treated for cancer. If a woman is diagnosed and treated for breast or ovarian cancer, she also retains a chance of dying from a non-cancer cause, or of developing the other cancer.

Model Probabilities

For this cost-effectiveness simulation model, we modeled the occurrence of events of interest (e.g. development of breast cancer), and the costs and quality of life associated with these occurrences. In order to determine the probabilities of these events occurring in the simulated cohort of women, a MEDLINE search was conducted to determine parameters from the published literature, when possible.

Natural History of Disease

Prevalence of mutations was taken from the medical literature on families with hereditary breast cancer. These women most closely match the experience of the Georgetown University Cancer Genetics program for counseling and testing women at risk. Prevalence of the mutation was subject to sensitivity analysis.

Both those women who have a susceptibility mutation and those who do not are at risk for both breast and ovarian cancer. Women without a mutation were assumed to develop these cancers at the same rate of those in the Surveillance, Epidemiology, and End-Results (SEER) tumor registry (Ries, et al, 2000). Those who have a susceptibility mutation were assumed to develop these two cancers at rates reported in the literature (Easton, et al, 1995; Ford, et al., 1994; Narod, et al., 1995; Struwing, et al, 1997; Whittemore, et al., 1997; Schubert, et al., 1997; Ford, et al., 1998). We assumed that the rate of other disease development and mortality was independent of susceptibility mutation status. Non-cancer mortality was taken from National Center for Health Statistics data.

We assume that, while women with susceptibility mutations were more likely to develop breast or ovarian cancer, that if these cancers developed, cancer- and stage- specific mortality was similar to those of women who had sporadic cancers. Age- and stage-specific survival was

determined from the SEER registry data (Ries, et al., 2000). For those women developing cancer, we assume that disease starts in-situ or in locally invasive stages, and that each year the disease has a probability of being detected through screening (if performed) or through clinical surfacing by developing signs or symptoms.

Progression probabilities of undiagnosed disease for breast cancer was determined using data from randomized clinical trials of breast cancer screening in which stage distributions of disease were available for the screened and unscreened arms. A Markov model was fit to these trials to determine the transition between stages during the preclinical interval between screen detection and clinical surfacing. The transition probabilities from this model were then used to model the progression through stages of disease prior to detection through screening or clinical surfacing. Parameters for ovarian cancer were adapted from the work of Skates and colleagues (1995).

Mutation Testing and Management

Sensitivity and Specificity for full gene sequencing were estimated using Myriad Genetics internal data on accuracy of testing. The sensitivity and specificity represent the accuracy for truly carrying a high-risk mutation; thus, not all women with a mutation will get cancer. The probability of choice of management options are derived from the choices of a cohort of women who have tested positive for a BRCA1 or BRCA2 susceptibility mutation in Georgetown University's Cancer Assessment and Risk Evaluation (CARE) program (Lerman, et al., 1996). The impacts of prophylactic mastectomy on the risk of breast cancer are derived from a cohort study of prophylactic mastectomy (Hartmann, et al., 1999). While data suggest a reduction of risk of development of ovarian cancer in women with oophorectomies (Struewing, et al., 1995), the risk reduction is less than 100%. We estimated this reduction in risk based upon

prior clinical consensus (Schrag, et al., 2000). We also assumed that prophylactic oophorectomy would reduce risk of breast cancer, based upon observational data from Rebbeck and colleagues (1999). We assumed that those women who had a prophylactic mastectomy would receive no further breast cancer risk reduction from oophorectomy. Impact of chemoprophylaxis is derived from the NSABP P-1 trial (Fisher, et al., 199X). Accuracy of breast and ovarian cancer screening tests were derived from the literature.

We assume for the baseline analysis that all women assigned to a particular management option are 100% compliant with the management option. This assumption is examined in sensitivity analysis.

Model Costs

The costs of providing counseling and testing are based upon a time-motion study of counselors and patients in the Lombardi Cancer Center Cancer Genetics Program (Lawrence, 1999). The cost of testing for the baseline analysis is based upon the estimated cost to provide full gene sequencing of the BRCA1 and BRCA2 genes (Lawrence, 1999).

The cost of diagnosis and treatment of breast cancer were derived from SEER-Medicare linked data, which links Medicare expenditures to individuals in the SEER registry. Ovarian cancer costs were derived from published data from a managed care organization (Fireman, et al., 199X). From these data sets, we were able to aggregate data on cost of cancer care by age, stage at diagnosis, and treatment phase. Treatment phases include: 1) Initial phase (the first 6 months after diagnosis), 2) Continuing Care phase (time between initial and terminal phases), and 3) terminal phase (last 12 months prior to death). Breast cancer SEER-Medicare data were provided by J. Warren (personal communication). Costs for prophylactic mastectomy and prophylactic oophorectomy were represented by literature data on cost of mastectomies (ref) and

abdominal hysterectomies and salpingo-oophorectomies (Van Den Eeden, et al., 1998). Cost of screening was based upon Medicare reimbursement for one office visit per year, plus screening mammography (for breast cancer) and transvaginal ultrasound plus CA-125 testing (for ovarian cancer). Cost of tamoxifen chemoprophylaxis was based upon the average wholesale price of tamoxifen (Redbook, 2000) plus 4 office visits per year for monitoring.

Model Utilities

Utilities for relevant health states were obtained by telephone survey of women at high risk for having a BRCA mutation who were participating in the Georgetown University Cancer Genetics Program. Utilities are measures of preference for a state of health that allow an individual to place a valuation on the quality of life associated with a state of health. Utilities were obtained using a linear rating scale (LRS) assessment technique (Froberg and Kane, 1989) for the relevant breast and ovarian cancer outcomes. The average LRS for current health of those women without a history of breast or ovarian cancer was used to represent the utility of not having cancer in the model. Utility for prophylactic mastectomy without cancer was represented by assessed utilities of prophylactic mastectomy with early breast cancer; this assumption is a conservative assumption which will favor not performing counseling and testing. The LRS scores were transformed into estimated time trade-off utilities using the transformation function reported by O'Leary and colleagues (1995). These utilities were used as quality-adjustment weights with which to calculate outcomes in units of dollars per quality-adjusted life year.

Model Analysis

The outcome of this cost-effectiveness analysis is the incremental cost-effectiveness (CE) ratio, expressed in units of cost per life year (LY) saved and cost per quality-adjusted life year

(QALY) saved. The incremental CE ratio is a measure of economic efficiency, and represents the amount of resources (in health care dollars) required to produce a unit of outcome (in LY or QALY); thus, lower CE ratios are more desirable. The CE ratio for two alternatives, A and B, is calculated by the equation:

$$CE\ Ratio = \frac{Cost_A - Cost_B}{LY_A - LY_B}$$

Sensitivity Analyses

Sensitivity analyses, or varying a parameter over a range to determine the impact on the outcome, were conducted for all relevant variables. These analyses allowed us to examine changes in the assumptions about the values of individual parameters. We report the analyses that had the largest impacts on model results.

RESULTS

Model Parameters

The parameters used in the model are shown in the Appendix. Key findings from the parameters show that in our modeled high-risk population, the prevalence of BRCA1 and BRCA2 mutations was high (15.5% and 6.7%, respectively). The cost of providing counseling only was \$208 per person counseled, and the cost of both counseling and testing using full gene sequencing of BRCA1 and BRCA2 genes was \$2052. Women in the Lombardi Cancer Center Genetics Program who tested positive frequently had not had prophylactic procedures; only 2.3% had a prophylactic mastectomy only, 16.4% had a prophylactic oophorectomy only, and 6.3% had both procedures.

Model Prediction for Breast Cancer

Figure 3, shows the model prediction for breast cancer incidence for the US general population (equivalent to setting the BRCA1/2 prevalence to 0 in our model), compared to 1992-1996 SEER registry incidence data. The model results assume current US mammographic screening rates. Overall stage distributions at detection are (SEER vs. model) 67.7% vs. 67.6% local stage breast cancer, 26.3% vs. 27.2% regional stage breast cancer, and 5.9% vs. 5.2% distant stage breast cancer.

Cost-Effectiveness of Counseling and Testing

Table 1 shows the incremental cost-effectiveness results for counseling and testing an 18 year old and a 45 year old high risk woman without breast cancer. Strategies are arranged from least expensive (Routine Care) to most expensive (Counseling + Testing), and incremental cost-effectiveness ratios are given compared to the next least expensive strategy. The costs and life-years presented in the table were discounted to present value at 3%. Both counseling and counseling plus testing saved life years for both 18 year olds and 45 year olds. The undiscounted average gain in life expectancy per woman for counseling and testing compared to routine care was 0.489 years (5.8 months) for the 18 year olds and 0.177 years (2.1 months) for 45 year olds. Discounted life years saved were smaller due to the gains occurring in the future. Costs were also increased for both the counseling and counseling plus testing arms compared to the routine medical care arm. The incremental cost-effectiveness ratios of counseling and testing vs. routine care were \$27,416/LY and \$42,717/LY for 18 years old and 45 years old, respectively. The incremental cost-effectiveness ratios counseling plus testing were below our \$50,000/LY

threshold in both cases, although counseling only for 45 year olds was greater than \$50,000/LY, it remained less than \$100,000/LY.

Sensitivity Analyses

Sensitivity analyses are performed to explore the impact of changes in assumptions about parameters on the results and conclusions of the model. We present the sensitivity analyses by asking a series of questions about the relevant parameters in the model.

What happens if women who test positive receive different management procedures?

The cost-effectiveness of counseling and testing are sensitive to the method for management chosen by women who test positive for a BRCA1 or BRCA2 susceptibility mutation. Based upon the CARE cohort, few women who test positive for a susceptibility mutation undergo prophylactic bilateral mastectomy. If all women who tested positive for a mutation underwent a prophylactic mastectomy, then the counseling and testing strategy would increase discounted life expectancy by 0.107 LY for 45 year old women, for an incremental CE-ratio of \$23,262/LY compared to routine care. If all women who tested positive for a susceptibility mutation chose to have both prophylactic mastectomy and oophorectomy, then the CE-ratio for counseling and testing would decrease to \$17,626/LY compared to routine care. Using data on management choice for a cohort of women who were more likely to choose a prophylactic surgery (Meijers-Heijboer, et al., 2000) than our baseline analysis, the incremental cost-effectiveness ratio would be \$24,509/LY.

What if screening adherence is not ideal?

In our baseline analysis, we assume that women are perfectly adherent to screening regimens. This is an idealized assumption which may make screening look more effective than it actually is. Lerman and colleagues (2000) reported 1-year breast cancer screening rates of 64%-75% in carriers, dependent on age. If we assume that those in the usual screening arm undergo screening at rates consistent with the general population (MMWR, 1999), and that those who choose intensive screening have a 70% probability of attending any particular screening session, then the CE-ratio actually improves to \$33,619/LY for a 45 year old woman. This is due to a relatively larger drop in life expectancy from baseline analysis in the routine care arm compared to the counseling and testing arm from less frequent screening.

What if the prevalence of BRCA1 and BRCA2 mutations is different?

The cost-effectiveness of counseling and testing is quite sensitive to the prevalence of BRCA1 and BRCA2 susceptibility mutations in the cohort being tested, since those without the mutations will receive no life expectancy benefit from testing. If the prevalence of susceptibility mutations is one-half of our baseline value, then the CE-ratio increases to \$101,448/LY for a 45 y.o. woman. As prevalence increases, conversely, the cost-effectiveness decreases. For example, if mutation prevalence is doubled from our baseline values, then the cost-effectiveness ratio decreases to \$12,493/LY.

What if quality of life is considered?

We examined the impact of quality of life in addition to length of life by adding utilities, or quality adjustment weights, for health states as shown in the Appendix. If we include these utilities, then counseling and testing saves 0.038 QALYs (discounted), and the cost-effectiveness ratio increases to \$72,330/QALY compared to routine care.

DISCUSSION

Women with BRCA1 or BRCA2 susceptibility mutations are at high risk of developing breast and ovarian cancer. While options for managing this cancer risk are available, the genetic counseling and testing necessary to identify women with BRCA1/2 mutations are expensive, thus the number of women needed to be tested to correctly identify a susceptibility mutation has a large impact on the cost-effectiveness of counseling and testing. We have found in this analysis that testing women who are without known cancer and who are at high risk for carrying a mutation has a high cost, but also a large benefit, making counseling and testing cost-effective in this group. The cost-effectiveness ratio is quite sensitive to prevalence of the mutations, however, so in lower-risk groups the costs may not be justified by the outcomes.

Cost-effectiveness of counseling and testing also is very dependent on which options women who test positive for BRCA1/2 mutation choose to manage their cancer risks. In our baseline case, the majority of women do not choose prophylactic surgery. This case is modeled after a cohort of women facing such choices, however others have reported much greater uptake of prophylactic surgery (Meijers-Heijboer, 2000). As other decision analyses (Schrag, 1997; Grann, 1998) have concluded, our model predicts a greater life expectancy impact for prophylactic surgery compared to screening. Thus, as more women receive prophylactic mastectomy, which is modeled as having the greatest breast cancer risk reduction (Hartmann, 1999), the life expectancy benefit of testing becomes greater, and counseling and testing accordingly becomes more cost-effective. Choice of management strategies interacts with prevalence to determine cost-effectiveness; as more women choose prophylactic surgery as a management option, counseling and testing become cost-effective for lower prevalences of

mutation. Thus, future research should be directed at understanding women's preferences for cancer risk management options for those who test positive for a susceptibility mutation, and ensuring women make choices consistent with their preferences. If women's preferences are to choose prophylactic surgery then counseling and testing may be cost-effective at lower prevalences. On the other hand, if women are more likely to prefer screening over prophylactic surgery, then testing should be reserved for higher prevalence groups.

The cost-effectiveness of the counseling only strategy is more variable than that of counseling and testing. Cost-effectiveness of counseling is highly dependent on what options women who undergo counseling choose for risk management. That this strategy is more sensitive to choice of management options than the counseling and testing strategy makes intuitive sense; in the counseling only strategy all women who are counseled need to choose between the different management options, whereas only those who are identified with a susceptibility mutation are modeled as choosing between decision options of prophylactic surgery or intensive screening in our model. If women who were tested and not identified as having a susceptibility mutation still underwent intensive screening or prophylactic surgery, then the counseling and testing strategy would be less cost-effective compared to counseling only then our baseline results would suggest.

Including quality of life in the analysis did reduce the cost-effectiveness ratio to some extent. In this analysis, we use a worst case scenario for the utility for prophylactic mastectomy and oophorectomy, by assigning them the utility women have given for prophylactic mastectomy with local breast cancer. As this utility is increased, counseling and testing become more cost-effective. Thus, women who have extremely low utilities for health states involving prophylactic surgeries may receive less benefit as measured in QALYs compared to women who do not have low utilities.

Our analysis has several caveats. First and foremost, there has never been a randomized clinical trial demonstrating survival or quality of life benefit to genetic counseling and testing compared to not testing. The data that inform our model are based primarily upon observational studies, and thus are more open to possible biases than data from randomized trials. However, these data are the best data available to inform the model. Second, we assume that women are perfectly adherent to treatment and screening regimens. We assumed this to ensure an equal representation of benefit across strategies; however, in sensitivity analysis, if we use actual screening rates, the cost-effectiveness of counseling and testing compared to routine care improves. Next, we ignore the issue of family members with mutations. If a woman is a member of a cancer family due to a known susceptibility mutation, she may need only be tested for a single mutation rather than full gene sequencing. While this would not reduce the cost of counseling, it would reduce the cost of testing, making offering counseling and testing more cost-effective. Finally, we do not address the issue of counseling and testing in women already diagnosed with breast or ovarian cancer. While women with susceptibility mutations are more likely to develop breast cancer than those who do not have a mutation, and are more likely to develop a second breast primary, it is uncertain that breast cancer survival for carriers is poorer than that of women with sporadic breast cancer. Work addressing the issue of counseling and testing women with known cancer is currently ongoing.

Within these limitations, we conclude that the benefits of offering counseling and testing to women at high risk of carrying a breast cancer susceptibility mutation justify the costs involved. While counseling and testing high-risk women is cost-effective, offering these services becomes dramatically less cost-effective as prevalence decreases. Since prophylactic surgery has a larger impact on outcomes in our model than intensive screening, as higher

percentages of women testing positive for a susceptibility mutation choose prophylactic surgery, particularly mastectomy, counseling and testing become more cost-effective.

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Table 1. Costs and Benefits of Counseling and Testing.

Strategy	Cost	LY	Incr. Cost	Incr. LY	CER \$/LY
<i>18 y.o.</i>					
Routine Care	\$5346	27.7008			
Counseling Only	\$7864	27.7513	\$2518	0.0504	\$49,918
Counseling + Testing	\$8443	27.8138	\$579	0.0625	\$9258
<i>45 y.o.</i>					
Routine Care	\$8336	21.2476			
Counseling Only	\$10,384	21.2715	\$2048	0.0239	\$85,673
Counseling + Testing	\$11,106	21.3124	\$721	0.0409	\$17,626

Figure 1. Initial decision tree for genetic counseling and BRCA1/2 testing.

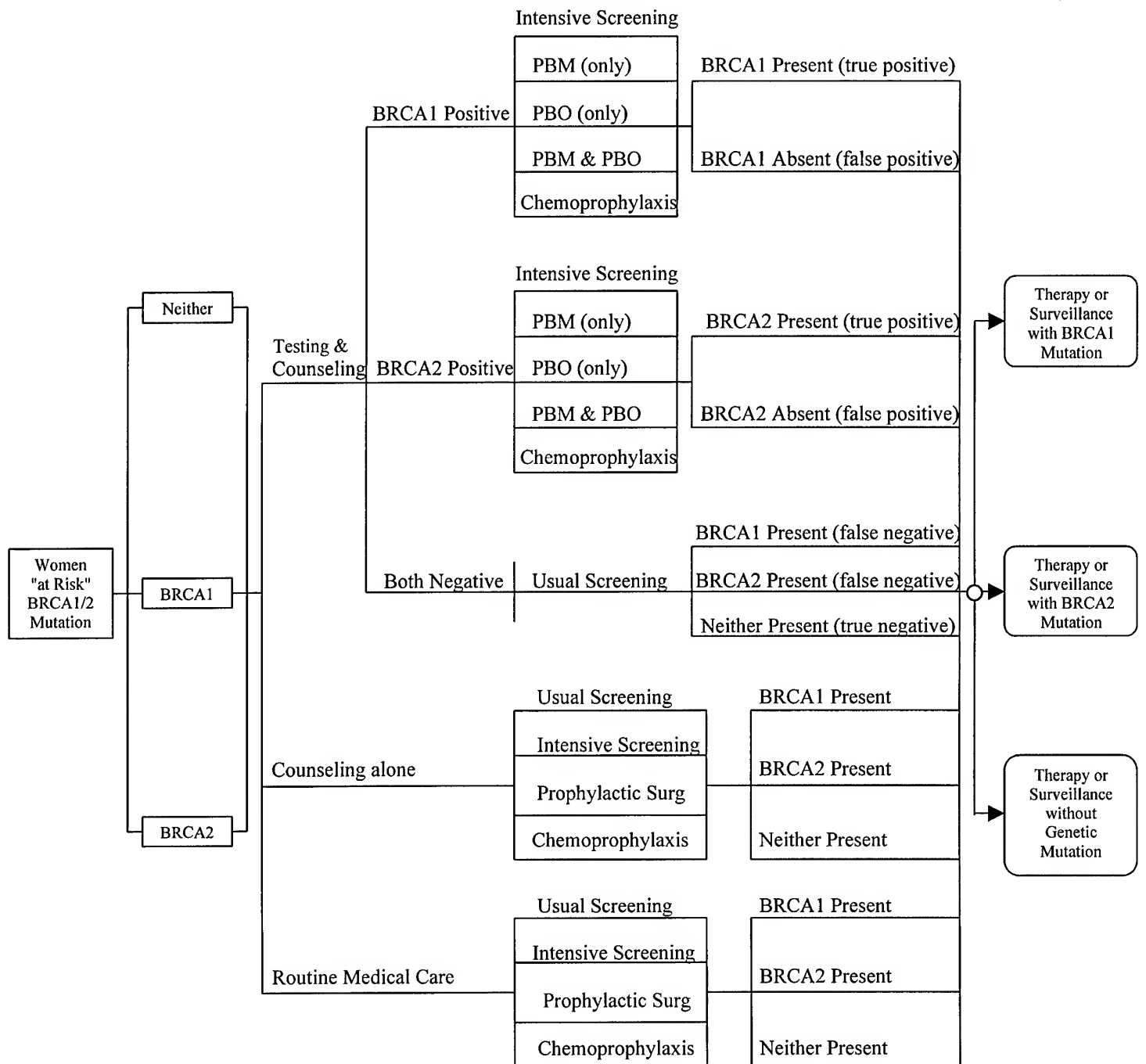


Figure 2. Flow diagram of natural history model, including development of breast and ovarian cancer.

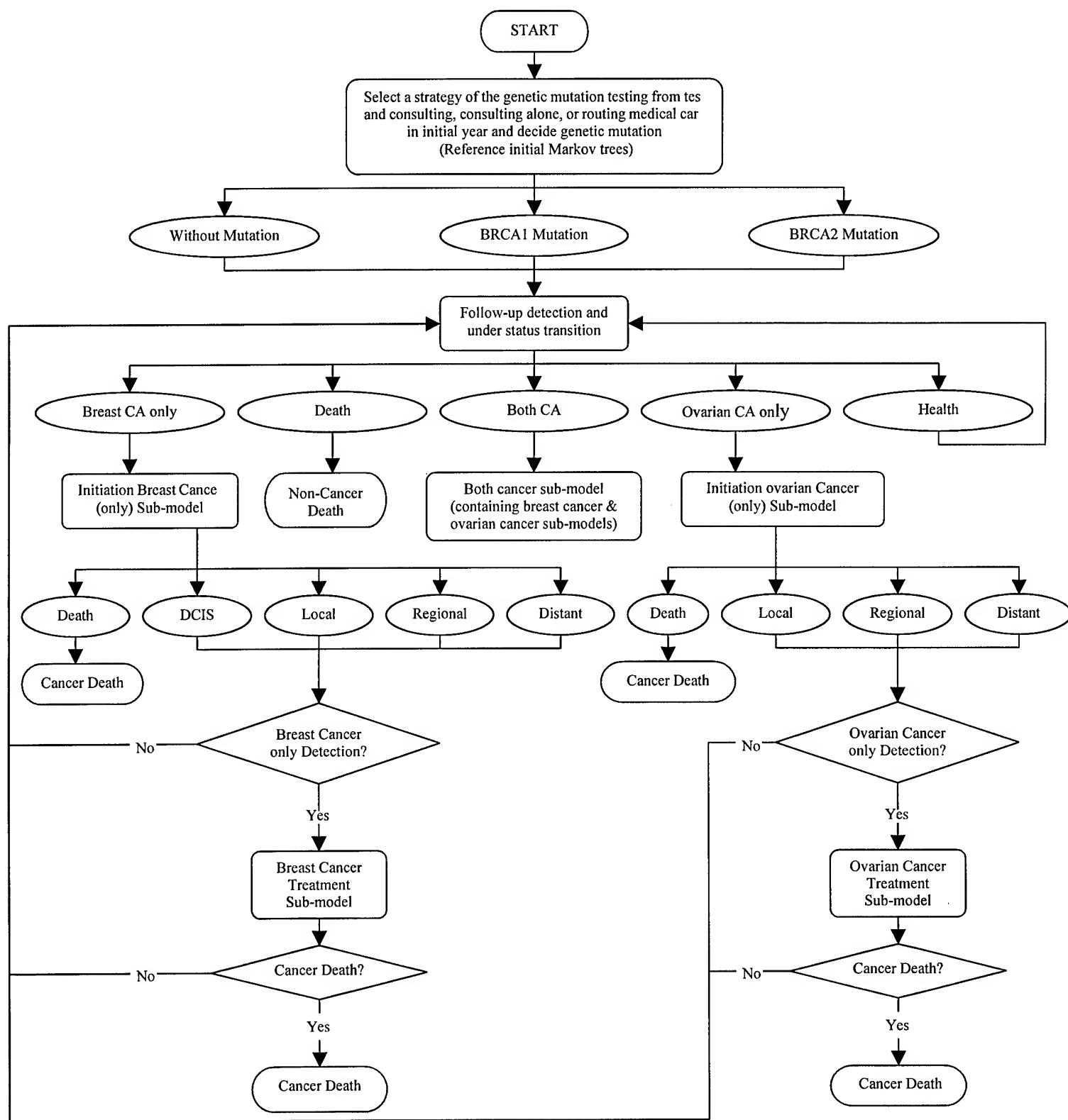
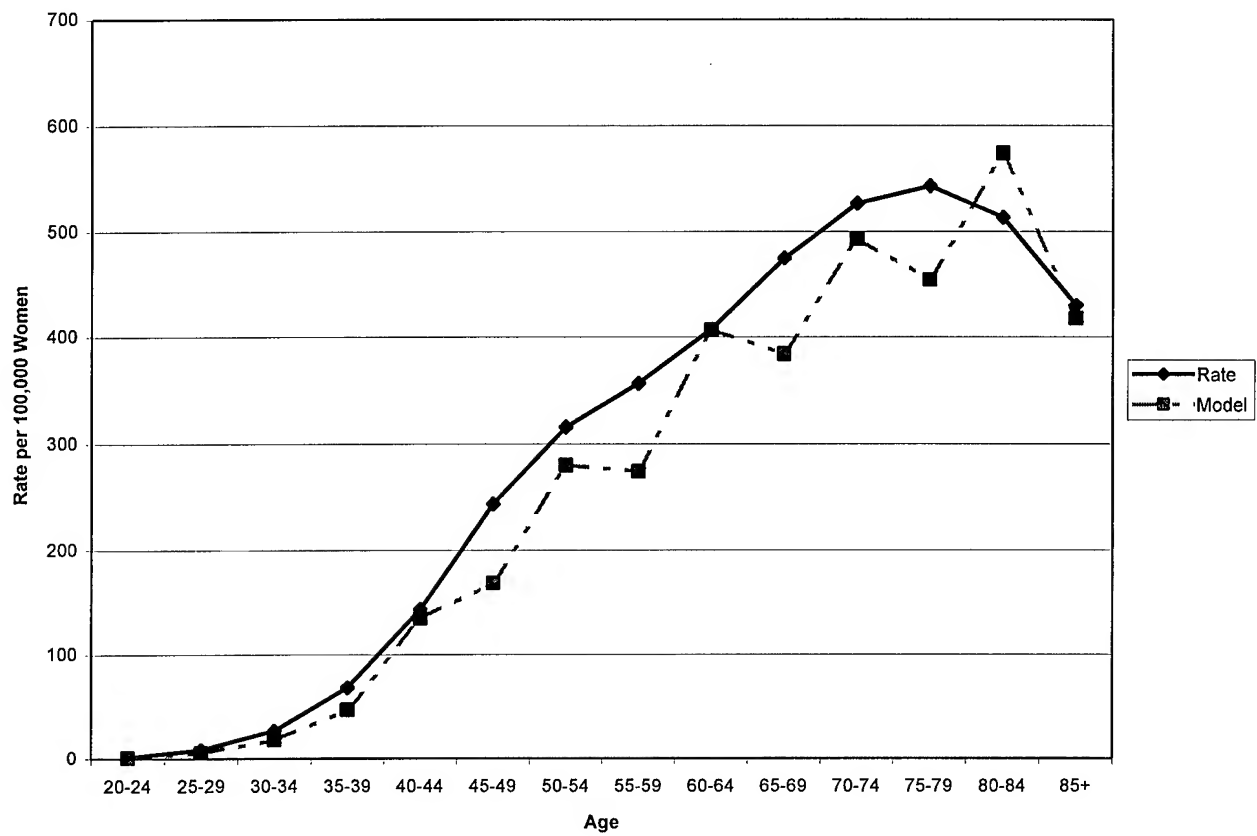


Figure 3. Model prediction of breast cancer vs. SEER registry for US population.



APPENDIX: PARAMETERS USED IN ANALYSES

Parameter	Estimate (Range)	Sources
Initial Tree		
Prevalence of BRCA genes		
General population BRCA1	0.778	
High-risk population BRCA1	0.155	
BRCA2	0.067	
Sensitivity of full gene sequencing	98% (85 ~ 100%)	Myriad Genetic Laboratories, 1998
Specificity of full gene sequencing	99% (98 ~ 100%)	Myriad Genetic Laboratories, 1998
Probability of prophylactic bilateral mastectomy given BRCA+ results	0.023	Georgetown University Cancer Genetics Program
Probability of prophylactic bilateral oophorectomy given BRCA+ results	0.164	Georgetown University Cancer Genetics Program
Probability of prophylactic bilateral mastectomy and oophorectomy given BRCA+ results	0.063	Georgetown University Cancer Genetics Program
Probability of receiving Tamoxifen chemoprophylaxis, given BRCA+ results	0.10	Clinical Opinion
Probability of usual breast cancer screening in counseling only arm	0.67	Clinical Opinion
Probability of intensive breast cancer screening in counseling only arm	0.20	Clinical Opinion
Probability of prophylactic bilateral mastectomy in counseling only arm	0.01	Clinical Opinion
Probability of prophylactic bilateral oophorectomy in counseling only arm	0.01	Clinical Opinion
Probability of prophylactic mastectomy and oophorectomy in counseling only arm	0.01	Clinical Opinion
Probability of chemoprophylaxis in counseling only arm	0.10	Clinical Opinion
Disease Initiation Model		
Initial distribution of breast cancer		
General population*		
DCIS		SEER DCIS incidence, 1992-96
Local stage		SEER DCIS incidence, 1992-96
For women with PBM		
Local stage	0.25	

Regional stage	0.75	
Stage distribution of breast cancer		
General population*	Age dependent	SEER incidence by stage, 1992-96
Initial distribution of ovarian cancer		
General population		
Local stage	100%	
For women with PBM		
Regional stage	100%	
Stage distribution of breast cancer*		
General population	Age dependent	SEER incidence by stage, 1992-96
Population all-cause mortality*	(0.001 ~ 0.059) [□]	Statistics Abstract of the United States, 1995
Breast cancer incidence		
Cumulative probability of BRCA1 (+)*	10.4% ~ 73.5%	Whittemore, 1997 (by age)
Cumulative probability of BRCA2 (+)*	10.4% ~ 73.5%	Whittemore, 1997 (by age)
BRCA1/2 (-)*	(0.00001~0.00483)**	SEER, 1992-1996
After prophylactic bilateral mastectomy	0.1 * baseline	Hartmann, 1999
Ovarian cancer incidence		
Cumulative probability of BRCA1 (+)*	4.0% ~ 27.8%	Whittemore, 1997 (10-year age group)
Cumulative probability of BRCA2 (+)	0.000425-0.0236	Ford, 1998 (10-year age group)
BRCA1/2 (-)*	(0.00001~0.00062)**	SEER, 1992-1996
Breast cancer stage transition without treatment (yearly transition probability)		
DCIS to DCIS	0.714	See Methods
DCIS to Local	0.286	
Local to Local	0.828	
Local to Regional	0.172	
Regional to Regional	0.958	
Regional to Distant	0.042	
Ovarian cancer stage transition without treatment (yearly transition probability)		
Local to Local	0.397	Skates, 1995
Local to Regional	0.603	
Regional to Regional	0.159	
Regional to Distant	0.841	

Surveillance ¹		
Breast cancer		
Mammography / CBE		
Sensitivity	82.8 % (74 ~ 88%)	Shapiro, 1988; Chamberlain, 1991; Miller, 1992; Fletcher, 1993
Specificity	98.7% (97.7 ~ 99.8%)	Shapiro, 1988; Chamberlain, 1991; Miller, 1992; Fletcher, 1993
Ovarian cancer		
Conventional transvaginal ultrasound		
Sensitivity	81.6% (0 ~ 100%) weighted mean= 89.3% (3.05)	Grover, 1995; DePriest, 1997; Bourne, 1993; van Nagell Jr., 1991; Franchi, 1995; Hata, 1992; Zantta, 1994; Weiner, 1992; DePriest, 1994;
Specificity	81.4 % (65.4~ 98.7%) weighted mean= 97.5% (1.79)	
Doppler transvaginal ultrasound		
Sensitivity	89.9%(75.7~100 %) weighted mean= 88.3% (2.27)	Franchi, 1995; Hata, 1992; Kawai, 1992; Zanetta, 1994; Weiner, 1992; Caruso, 1996; Vuento, 1995; Kurjak, 1992; Tepper, 1995; Bourne, 1993
Specificity	86.9 % (52.8 ~ 99.2%) weighted mean= 92.4% (2.54)	
CA-125		
Sensitivity	79.7% (44.4 ~ 100%) weighted mean= 75.7% (4.29)	Franchi, 1995; Maggino, 1994; Jacobs, 1994; Helzlsouer, 1993; Soper, 1990; Hata, 1992; Kawai, 1992; Zanetta, 1994; Peters, 1995; Gadducci, 1996; Weiner, 1992; Jacobs, 1992; Zurawski, 1990; Grover, 1995
Specificity	77.7 % (40.0~100.0%) weighted mean= 90.7% (2.73)	

Breast cancer natural history		
Incidence of breast cancer by age and stage		SEER, 1992-1996
Probability of DCIS to invasive breast cancer	5% (yearly rate)	Page, 1982
Ovarian cancer natural history		
Incidence of ovarian cancer by age and stage		SEER, 1992-1996
Health State Utilities		
Health State	Utility	
Healthy without Cancer or Prophylactic Surgery	0.97	
Prophylactic Bilateral Mastectomy, No Cancer	0.92	
Prophylactic Bilateral Oophorectomy, No Cancer	0.92	
Diagnosed and Treated DCIS	0.92	
Diagnosed and Treated Local Breast Cancer	0.92	
Diagnosed and Treated Regional Breast Cancer	0.88	
Diagnosed and Treated Distant Breast Cancer	0.65	
Diagnosed and Treated Local Ovarian Cancer	0.92	
Diagnosed and Treated Regional Ovarian Cancer	0.59	
Diagnosed and Treated Distant Ovarian Cancer	0.59	

* DEALE used to calculate annual age-specific transition probabilities.

□ Expected deaths over alive at specified age between 20 and 80 years old.

** Incidences of invasive breast or ovarian cancer in every 5 years from 20 to 85+ years old.

□ Data summarize the accuracy of screening for breast cancer and screening or diagnosis for ovarian cancer.

□ Derived from the 5-year survival rate of distant breast cancer.

=sensitivity is weighted by number of cancer cases; specificity is weighted by number of non-cancer cases.

**HEALTH PREFERENCES OF WOMEN AT HIGH-RISK FOR BREAST CANCER
GENETIC SUSCEPTIBILITY MUTATIONS**

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Funding: This work was funded by Contract DAMD 17-96-C-6069, "Breast Cancer Center Contract", by the Department of the Army

ABSTRACT

Background: Women carrying a BRCA1 or BRCA2 breast cancer genetic susceptibility mutation are at high-risk of developing breast and/or ovarian cancers. Options available to manage this risk may involve trade-offs of current quality of life in order to reduce cancer risk.

Purpose: To understand the health preferences women at high-risk of carrying a BRCA1/2 mutation place on health states involved in cancer risk management decisions.

Methods: Women enrolled in a cohort study of genetic counseling and testing for BRCA1/2 mutations received a telephone survey assessing rating scale (RS) preferences for the following health states: breast conserving surgery (BCS), modified radical mastectomy (MRM), and prophylactic bilateral mastectomy (PBM) for early stage breast cancer, breast cancer recurrence, metastatic breast cancer, advanced ovarian cancer, and current health. Utilities for current health were also obtained using the Health Utilities Index (HUI).

Results: 587 women were surveyed. RS scores for the three surgical methods for treatment were high (BCS: 81.9, MRM 80.9, PBM 80.9), and were not significantly different. Women with breast cancer rated these three health states higher than those without breast cancer, but within each group the ratings for the three states were not significantly different. Utilities for more advanced cancers were lower, and did not vary by breast cancer status. Utilities for current health were lower for women with breast cancer compared to women without, but in multivariate analysis, breast cancer impact was minimal.

Conclusions: Women at high-risk of a susceptibility rating have a high utility for local breast cancer states, and have similar preferences for BCS, MRM, and PBM scenarios. Since preferences are quite similar, decision making for treatment of early preferences should be based on shared decision making that considers a woman's individual preferences.

INTRODUCTION

Quality of Life and Health Utility

The growing interest in the costs and quality of health care during the past decade has contributed to the dramatic growth of the field of outcomes research. One of the cornerstones of outcomes research is the measurement of quality of life (QOL). Clinical outcomes, or health effects of an intervention can be measured in terms of intermediate clinical outcomes such as time to progression or cancer cases detected, or as the more distal outcome of survival (years of life), or quality-adjusted life years (QALYs). To quality-adjust outcomes, measures of preferences for health outcomes are necessary, reflecting the fact that individuals with similar ability (or disability) to function may value that level of functioning differently. This measure is broadly referred to as a "utility" or "preference" value or weight.

Utility Measures

There are many areas of debate among methodologists concerned with measuring utility (Gold et al, 1996b; Mandelblatt and Eisenberg, 1996; Cox et al, 1992; Mehrez and Gafni, 1989;1993; Gafni and Birch, 1995; Ganz, 1994b; Dean, 1990; Slevin et al, 1990; Torrance, 1976b; 1982; 1987; Fryback et al, 1993; Nease et al, 1995; Wolfson et al, 1992). The most frequently used methods to assess individual preferences are time tradeoff (TTO), rating scale (RS), and standard gamble assessments. In this study, we used TTO and RS to assess women's individual utilities. In this way, we were able to compare utilities measured by these two

methods. In addition, the Health Utility Index (HUI) was used to measure utilities from a societal perspective.

The above two utility assessments provide a holistic assessment of the respondents personal preferences for a state of health. The HUI is a brief questionnaire that can estimate societal utilities from a societal perspective based upon ratings of several domains of health-related quality of life (sensory perception, mobility, emotional function, cognitive function, self-care, pain, and fertility). This index has been broadly used, and population-based utilities are available (Torrance et al, 1972; 1984; Drummond et al, 1987; Ontario Ministry of Health, 1990).

Utilities in Hereditary Breast-Ovarian Cancer

Recent advances in molecular genetics have lead to the isolation of the BRCA1 and BRCA2 breast cancer susceptibility genes (Miki, 1994; Wooster, 1995). Mutations in these genes may account for up to 10% of cases of breast cancer (Claus, 1996), and are observed in a significant proportion of families with multiple cases of breast and ovarian cancer (Easton, 1995; Ford, 1998; Ford, 1994). Testing for mutations in these two genes is starting to be used in clinical practice (Cho, 1999), and is covered all or in part by some insurers.

Information obtained from genetic testing my enable women to make informed decisions about their medical management. Women who test positive for a BRCA1 or BRCA2 mutation have several options for cancer screening and cancer risk reduction, although long-term studies demonstrating the efficacy of these strategies is not yet available. These options may include intensive surveillance with breast and ovarian cancer screening initiated at an early age (Burke, 1997), chemoprophylaxis with agents such as tamoxifen (Fisher, 1998) or raloxifene

(Cummings, 1999) to reduce breast cancer risk, or prophylactic mastectomy (Hartmann, 1999) and/or oophorectomy to reduce breast and/or ovarian cancer risk. Prophylactic mastectomy may be performed for women without breast cancer or for women with breast cancer to reduce the risk of a second breast primary cancer.

Women deciding whether to partake in genetic counseling and testing and women who test positive and who are deciding on management options must weigh the risks and benefits of their choices. Women who have chosen to undergo testing have been reported to be quite variable in their rates of undergoing prophylactic surgery to reduce risk of breast and ovarian cancer (Lerman, 2000; Meijers-Heijboer, 2000). In order to choose a management option, women must implicitly or explicitly decide about their preferences for the outcomes associated with each option, including the quality of life of living with the results of the management option (e.g. having both breasts and/or both ovaries removed), and the resulting risk of cancer and the associated quality of life of living with breast or ovarian cancer. In order to better understand preferences for these outcomes, we studied the preferences for relevant outcomes in a group of women at high-risk for having a BRCA1 or BRCA2 mutations. The goals of this study were to: 1) describe the preferences for different health states potentially experienced by women with genetic susceptibility to breast and ovarian cancer; 2) to study the determinants of these preferences; and 3) to understand the determinants of preferences for current health in this population of women.

METHODS

Study population and procedures

Participants included women enrolled in a longitudinal study of people at high-risk of having a breast cancer susceptibility mutation. Eligibility criteria were developed to include those who had at least a 10% prior probability of carrying a mutation in either BRCA1 or BRCA2, which were consistent with published recommendations (the American Society of Clinical Oncology statement, 1996). The combination of age, breast and ovarian cancer status, family history of breast and/or ovarian cancer, and race (i.e., Ashkenazi Jews) made up the inclusion criteria (See Appendix). In addition to these criteria, relatives of the “Proband,” the first person receiving genetic testing in a family, who was identified with a BRCA1 or BRCA2 mutation, were invited to participate in the program. We limited our analysis to female participants to examine their perception of breast and ovarian cancer.

During 1996 to 2000, eligible women were identified through both physician referrals and self referrals. Participants first completed a baseline telephone interview that collected data on family history, medical history, risk factors, and psychological well-being. After providing written informed consent, individuals participated in a counseling session before genetic testing. Results were disclosed during a subsequent genetic counseling session, where the HUI assessment was administered. Follow-up interviews to assess the outcomes of genetic testing were completed at 1, 6, and 12 months after testing (or declining test results). The TTO and RS were administered at baseline, and the RS at 6- and 12-month follow-up. Interviewers were trained to conduct TTO and RS assessments using the computer-assisted telephone interview (CATI) method.

Measures

The main measures of this study, health utilities, include RS and HUI assessments. TTO assessments were initially performed, but the assessment was discontinued due to poor reliability of assessments. Other variables included women's age, breast cancer status, ovarian cancer status, and BRCA1 and BRCA2 mutation status.

The TTO assessment provides a holistic assessment of the respondent's preference for a state of health. The TTO asks the respondent to make a choice between living for a specified time in the state of health of interest, or living for a shorter period of time in excellent health. For example, if a woman felt that living 30 years with a mastectomy for early stage breast cancer was as desirable as living 25 years in excellent health, her utility would be the ratio of the two times, $25/30=0.83$.

The RS preference assessment technique asks the respondent to directly rate the health states represented in the TTO scenarios on a scale from 0, representing death, to 100, representing the best state of health imaginable. The RS assessment technique used is similar to that of the EuroQOL (EuroQoL Group, 1990), modified for telephone administration.

The scenarios used in TTO and RS methods portrayed and measured utility for several of the key choices or treatments these high-risk women might face with (Singer et al, 1991; Yellen et al, 1994; McQuellen et al, 1995; Ashby et al, 1994). Seven scenarios were developed, including prophylactic bilateral mastectomy with local breast cancer, prophylactic bilateral oophorectomy with local breast cancer, mastectomy with local breast cancer, breast conserving surgery with local breast cancer, in-breast cancer recurrence, metastatic breast cancer, advanced ovarian cancer, and current health. Each scenario provided information about the woman (third person) in the scenario, the severity of the cancer, procedures for treatment/prophylaxis, and

possible side effects. These scenarios were validated by a clinical oncologist and pretested in women with high-risk of carrying BRCA mutation genes. The life expectancy used in the TTO assessments for hypothetical local diseases and for current health was 30 years, and five years for distant disease. A bisection technique was used to determine the indifference point. To lessen respondent burden, each participant receives three randomly selected scenarios for TTO and RS assessment. Two of the scenarios were chosen from mastectomy, breast conserving surgery, and prophylactic bilateral mastectomy to examine the values for surgical options available for local breast cancer; the third scenario was chosen from the rest of the scenarios. The TTO results are expressed on a scale from 0, representing death, to 1, representing excellent health, corresponding to the 1 to 100 range used in the RS assessment.

Th HUI measures sensory perception, pain, mobility and dexterity, emotional function, cognitive function, self-care, and fertility. This instrument has been validated, and has been able to show differences between breast cancer patients who have had mastectomy and breast conserving surgery (Feeny, et al., 1996). To minimize respondent burden, items or sub-items with low expected variability due to high ceiling effects as determined by results from a study on elderly breast cancer patients (Mandelblatt, JS, unpublished data). For example, questions asking women about their ability to walk and the ability to “understand when speaking the same language with strangers” were eliminated, and the score imputed from the breast cancer cohort. The final HUI version consisted of 14 items.

To determine the reliability of telephone administered TTO and RS assessments, we retested a convenience sample of 22 participants approximately 4 weeks after their baseline assessments, prior to receiving genetic counseling. Retests consisted of face-to-face interviews with a trained interviewer providing TTO and RS assessments on the same scenarios as

performed in the baseline telephone interview. The interviewer used a visual vertical rating scale, similar to the EuroQoL instrument (ref) for the RS, and a visual aid graphically showing time in each health state for the TTO.

Analysis

The analytical plan was guided by our research questions. First, to assess and compare health utilities, the mean values of TTO and RS were reported and the Pearson's correlation coefficient was used to compare TTO and RS scores in each scenario. Test-retest reliability to compare face-to-face versus telephone administration was calculated using Pearson correlation coefficients.

To assess the determinants of health utilities, we used t-tests to examine the influence of age, breast cancer status, ovarian cancer status, and BRCA mutation status on the RS score of each scenario and current health. Correlation analysis was used to examine the relationship between current health, measured by the HUI, and the RS score according to scenarios. In addition, the relationships between the HUI score and participants' age, breast and ovarian cancer status, and mutation status were examined using t-test statistics. Finally, a multi-variate generalized linear model was used to examine the relative importance of age, cancer status, mutation status, and current health in RS and HUI scores.

The HUI scores were calculated using the HUI Mark II algorithm (Furlong et al, 1996). For questions not included in the survey due to low variability, we assigned the same values to each participant based on the most frequent answers (usually >99%). The final score ranged from 0 (death) to 1 (excellent health).

Because the BRCA testing results were not available at the baseline assessment, we compared the effect of mutation status on health utilities assessed before (baseline) and after (6-month follow-up) results of genetic testing were disclosed.

RESULTS

Participant characteristics

Utility data were collected from 587 women. Their mean age was 49 (18-79). About 65% (N=384) had breast cancer and 9% (N=50) had ovarian cancer. Of those reporting having their breasts removed (N=224), only 3% done so for preventive reasons. In contrast, those reporting having ovaries removed (N=146), 33% were for preventive reasons. About 55% (N=321) tested positive for BRCA mutation, and 24% declined the test.

Face-to-Face vs. Telephone Administration Reliability

A convenience sample of 22 women underwent both baseline telephone administration and face-to-face administration of the utility assessments. Test-retest reliability for the RS was 0.75, while the reliability for the TTO was only 0.35. TTO assessments were discontinued on completion of the reliability study due to poor correlation, data are available on approximately one-third of the study cohort.

Utilities measured by RS and TTO

While TTO scores are reported, we focus mainly on RS scores in this analysis. Table 1 shows results for utilities for the hypothetical states of health and perceived current health. Briefly, these results consistently showed that participants tended to have higher utilities

measured with the TTO compared to the RS. The utilities for early breast cancer were quite high, similar to average utilities for current health for the cohort. These high scores of utilities were not responsive to changes across the three modes of treatment; utilities for mastectomy, breast conserving surgery, and prophylactic mastectomy were not significantly different. RS assessments showed a decrease in the utility for in-breast recurrence, and an even larger decrease in utilities for metastatic breast cancer and for advanced ovarian cancer. None of the correlation between TTO and RS assessments was statistically significant.

Predictors of Utilities

The effects of age, cancer status, mutation status, and current health on health utilities are shown in Table 2. Women without breast cancer rated their health significantly higher than those with breast cancer; however, women with breast cancer tended to rate the scenarios for early breast cancer (prophylactic mastectomy, breast conserving surgery, modified radical mastectomy) higher than women without breast cancer. Those who had ovarian cancer rated also prophylactic mastectomy higher than those without ovarian cancer. Having a BRCA1 or BRCA2 mutation was related to a high score in mastectomy. Current health assessed by RS and HUI were significantly correlated ($r=0.338$, $p < 0.01$). The HUI, reported by 429 participants, showed a significant decrease with age, with participants under age 40 averaging 0.66 and participants age 40 and older averaging 0.64.

In multi-variate analyses (Table 3), having breast cancer was associated with a positive impact on utilities of breast cancer surgery and two prophylactic procedures and its negative effect on current health. Older age was associated with a lower utility for recurrent breast cancer ($p=0.03$) and current health ($p=0.01$). Better current health was associated with higher utilities

for mastectomy ($p=0.03$) and prophylactic mastectomy ($p=0.006$). Women who tested positive for BRCA1 or BRCA2 susceptibility genes tended to have lower utilities for their health and for mastectomy compared to those without mutation. The average utility for each health state before the disclosure of genetic testing results did not differ significantly after results were given (Table 4).

DISCUSSION

The women in this study, who are at high risk for having a BRCA1/2 susceptibility mutation, rated the health states involving local breast cancer quite high as assessed by both the RS and TTO measures. For example, Unic, et al., (1998) in a study of high-risk women without breast cancer, found a rating scale preference for the state of having a prophylactic mastectomy without breast cancer to be 0.5, much lower than our participants rated having a prophylactic mastectomy with local breast cancer. Utilities for breast cancer declined as the stage and severity of breast cancer increased. Similarly, advanced ovarian cancer received a low utility rating similar to that seen in metastatic breast cancer.

Both RS and TTO scores showed little variation by type of treatment for local breast cancer: BCS, in which the tumor is removed but the majority of breast tissue is preserved, modified radical mastectomy, in which the entire breast is removed and an axillary node dissection is performed, or prophylactic bilateral mastectomy, in which a modified radical mastectomy is performed on the breast with the tumor, and a simple mastectomy is performed on the contralateral breast. While RS scores were different between those participants with breast cancer and those without, within each group the RS scores were quite similar for all three

options. We hypothesized that RS scores would be higher for the breast sparing procedure due to the preservation of body image; data from this study did not support this hypothesis. In other work, Ashby and colleagues (1994) found that while doctors and nurses tended to rank early breast cancer scenarios with breast conserving therapy over ones with mastectomy, data for a small sample of breast cancer patients was less consistent. Thus, issues associated with having breast cancer or being experienced with breast cancer through being a member of a hereditary breast-ovarian cancer family may ameliorate the impact of breast conservation on preference; further work is needed to study the impact of cancer experience on the perceived trade-offs between breast conservation and cancer risk.

The preferences did perform as expected in that preferences were lower for more advanced cancer states. Utilities dropped significantly for the recurrence scenario and the advance breast and ovarian cancer scenarios.

One of the major determinants of the utilities for the early breast cancer scenarios was whether or not the participant had breast cancer. Experience with a health state may impact on the on the rating of the state (Ashby, 1994), although others have not found an impact (Llewellyn-Thomas, 1993). Controlling for other covariates, those with breast cancer rated the health states involving early breast cancer 6 to 10 points higher than those without cancer. While the coefficients were in a similar direction for the more advanced cancer scenarios, there were no significant differences in ratings for these health states between those with and those without breast cancer. Interestingly, for the metastatic breast cancer and advanced ovarian cancer scenarios the predictors we examined had no significant impact on utilities; scores for these scenarios were uniformly low.

TTO scores were consistently higher than RS scores. TTO and RS assessments in our sample are not highly correlated; and the TTO scores are inconsistent between phone and face-to-face administration. Participants reported having difficulty understanding the TTO probing questions that compare years of life living with perfect health and a specific health state. Using decision aids to administer TTO may improve women's understanding, which may indirectly increase the correlation between TTO and RS. Our primary mode of administration of the preference measures was by telephone interview, while the gold standard is face-to-face interviewing. In this study, the TTO did not correlate well between face-to-face and telephone interviews while the RS did, causing us to discontinue the TTO assessments during the study. Use of visual aids mailed to participants may increase reliability of phone assessments (van Wijck, et al., 1998), although our data emphasize the need to validate phone-based assessments. Anecdotally, we have in piloting found cognitive difficulties for some participants for the TTO assessments involving the issue of constant health states over time, which may impact on the reliability of the TTO for cancer assessments. In a standard TTO assessment, the participant is offered a choice between health state x for some fixed time t , or another state (usually excellent health) for a time less than or equal to t . Each option is offered as a certainty. When the health state is local cancer, offering 30 years of life with local cancer may be confusing to some participants because it negates the concerns about progression of disease, and early morbidity and mortality. On the other hand, to include risk of progression and death into the assessment negates the assumption of the TTO that the person is trading a fixed utility for health state x of duration time t for a specified period of excellent health. This is an important area for future clarification, specifically in regard to cancer health states. Since the RS assessments do not have

a future time component to the assessment, this issue of future uncertainty associated with the health states is less of a concern.

Several limitations should be considered when interpreting our results. First, women's understanding of breast and ovarian cancer-related health states are limited to the short description of each scenario. However, since most of the women in the study are either affected by breast cancer or have multiple relatives with breast and/or ovarian cancer, women in the study sample frequently have some direct or indirect experience with cancer health states. The wide range of each utility score, except for current health, may represent lack of enough information to make a judgment of preference, or may represent a wide range of preferences for outcomes across the cohort. While more specific scenarios, possibly with visual aids such as photographs or videotape sessions with cancer patients might decrease the variation in responses, the added specificity may compromise the generalizability of the assessment.

Second, our sample limited to primarily to women in the metropolitan Washington D.C. area. Thus, if regional differences exist, the generalizability of our results would be limited. In addition, participants may have different preferences from those not participating in the study. However, our data cannot differentiate this difference.

Third, the reasons for the difference in utility scores by age, cancer status, mutation status, and current health are not explored in our sample. Measures that will add information to explain our results include individuals' psychological and emotional state, personal preference, interaction with breast/ovarian cancer patients, health care utilization, the source of health-related information, and the influence of spouses.

In conclusion, this study provides an assessment of health utilities of women who are at high risk of having a BRCA genetic mutation. Modality used to treat early breast cancer did not

have a significant influence on utilities. Utilities decrease as the severity of cancer increases. Cancer status, mutation status, and current health are important modifiers of health utilities. Decisions between management options for having a susceptibility mutation involve trade-offs between immediate quality of life impacts of management strategies and the long-term risk of future cancer, and the health related quality of life associated with these cancers. Results of our study can be used to evaluate preferences for these outcomes, which will help women and policy makers to better understand the trade-offs between therapies and the impact of these therapies on women's preferences. Future research is needed to improve the assessment techniques and explore mutable barriers women may have toward each health state.

Table 1. Utilities assessed by Rating Scale and Time Trade Off, by scenario.

	MST	BCS	PBM	PBO	In-breast recurrence	Metastatic breast cancer	Ovarian cancer	Current health
Rating Scale (RS)								
N	379	377	386	116	128	115	105	113
Mean	80.9	81.9	80.9	78.8	71.7	48.6	42.8	81.6
S.D.	15.4	15.0	14.3	16.5	18.0	17.4	23.7	12.5
Range	0-100	0-100	20-100	0-100	10-100	10-90	0-95	50-100
Time Trade Off (TTO)								
N	111	115	122	36	43	35	27	32
Mean	0.906	0.929	0.920	0.915	0.875	0.575	0.653	0.910
S.D.	0.156	0.099	0.109	0.111	0.185	0.366	0.262	0.154
Range	0.003-1	0.5-1	0.5-1	0.5-1	0.003-1	0-1	0-1	0.43-1
Correlation with RS	-0.021	0.305	0.104	0.170	0.081	-0.081	-0.046	0.253

Table 2. Baseline Rating Scale/HUI

	MST	BCS	PBM	PBO	In-breast recurrence	Metastatic breast cancer	Ovarian cancer	Current Health
								RS
								HUI
Age (year, correlation coefficient)								
	0.027	-0.05	0.05	0.125	-0.181*	-0.03	-0.10	-0.140
Breast cancer								
Yes	83.1***	83.6**	83.0***	81.5*	71.8	49.8	44.1	79.2**
No	76.6	78.4	77.2	73.3	71.4	46.2	40.8	86.2
Ovarian cancer								
Yes	78.4	79.8	74.0**	77.2	70.6	49.2	36.0	78.0
No	81.2	82.0	81.5	79.0	71.8	48.5	43.1	82.0
BRCA mutation								
Yes	76.5**	79.6	81.3	74.1	73.2	50.3	43.8	80.1
No	82.8	82.7	81.3	81.6	70.0	47.9	43.4	80.9
Declined test	80.9	82.0	79.8	78.1	75.2	49.5	40.6	84.8
Current health (HUI) (correlation coefficient)								
	0.115	0.003	0.099	0.041	0.016	-0.065	0.127	0.338**
								1.0

* 0.01 < p ≤ 0.05

** 0.001 < p ≤ 0.01

*** p < 0.001

Table 3. Multi-Variate Regression Analysis of Impacts on RS and HUI Utilities

	MST (N=269)	BCS (N=275)	PBM (N=275)	PBO (N=80)	In-breast recurrence (N=88)	Metastatic breast cancer (N=85)	Ovarian cancer (N=75)	Current Health (HUI) (N=421)
Age	-0.06	-0.07	0.12	0.07	-0.38*	-0.13	-0.34	-0.001*
Breast cancer	7.04**	6.20**	7.21***	10.0**	4.66	3.05	8.77	-0.02**
Ovarian cancer	-0.11	-0.79	-7.05*	1.14	2.22	-1.70	-9.10	-0.003
BRCA mutation	-5.00*	-2.74	2.12	-7.84	3.25	3.47	5.64	-0.02*
Current health (HUI)	30.0*	5.60	30.1**	21.6	-5.73	-11.4	21.1	---

General linear model.

* 0.01 < p <= 0.05

** 0.001 < p <= 0.01

*** p <= 0.001

Table 4. Comparison of rating scales assessed at baseline and 6-month follow-up by mutation status.

BRCA mutation status	MST	BCS	PBM	PBO	In-breast recurrence	Metastatic breast cancer	Ovarian cancer
Baseline (N=587)							
Yes	76.5**	79.6	81.3	74.1	73.2	50.3	43.8
No	82.8	82.7	81.3	81.6	70.0	47.9	43.4
Six-month follow-up (N=247)†							
Yes	80.7	78.9	81.3	79.6	74.0	45.7	41.6
No	84.7	81.8	82.9	82.8	67.0	51.2	44.0

** significant difference (0.001 < p ≤ 0.01) between having and not having BRCA mutation at baseline.

† Utility scores assessed at baseline and 6-month follow-up were not statistically different in this sample.

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Acceptability of Diagnostic Tests for Breast Cancer

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Word count: 2,126
Number of tables: 4

Supported by Department of the Army Contract #17-96-C-6069 and Department of the Army Grant #17-94-J-4212.

ABSTRACT

Purpose: To assess the acceptability of new non-invasive breast cancer diagnostic tests.

Methods: Women who have abnormal breast physical examination, mammography, and/or standard sonography results and have been recommended to have a breast biopsy were invited to receive digital mammography, magnetic resonance imaging (Gd-DTPA enhanced MRI), and nuclear medicine evaluation (Tc-99m-sestamibi scanning) before biopsy. A self-administered questionnaire asked about women's satisfaction and acceptability with the procedures.

Acceptability for individual diagnostic tests was measured by self-reported discomfort, and embarrassment of each test and women's preference for tests as measured by the willingness to pay method.

Results: In general, participants (N=82) were satisfied with the process of receiving different diagnostic tests. Among those receiving the tests, 47% of those receiving MRI, 50% of those receiving digital mammography, and 66% of those receiving sestamibi imaging found the procedure more comfortable than a routine mammogram. Most of the participants did not feel embarrassed when receiving any of the diagnostic tests. Women who provided a response to willingness-to-pay questions (N=43) would pay an average of \$611 to have a test instead of a biopsy if the test is as accurate as biopsy. The willingness to pay significantly decreased to an average of \$308 in the case of 95% accuracy. Those who had prior benign breast diseases were less willing to pay for a test of 95% accuracy than those did not have benign breast diseases.

Conclusion: We conclude that women would find these tests acceptable, and would find the tests preferable to biopsy if they were equally accurate or nearly equally accurate at evaluating breast lesions as biopsy. New technologies to detect breast cancer should focus on decreasing discomfort as well as increasing test accuracy.

INTRODUCTION

There are estimated 600,000 breast biopsies performed annually in the US (Osteen et al, 1991); as many as 80% of these yield benign results (Winchester et al, 1983; Artz and Blume, 1991). Thus, the potential economic and quality of life (Gram et al, 1990; Parker, 1993) impact of alternative diagnostic pathways is substantial. Although new non-invasive technologies have continued to be developed to increase the accuracy of detecting breast cancer, few studies examined the acceptability of the technologies from the perspective of patients who received them.

The purposes of this project are two folds. The first is to assess the acceptability of new diagnostic technologies being evaluated from the patient's perspective. We focused on embarrassment and discomfort caused by the procedure. These included digital mammography, magnetic resonance imaging (Gd-DTPA enhanced MRI), and nuclear medicine evaluation (Tc-99m-sestamibi scanning). The second is to understand women's preferences for avoiding a biopsy in favor of a non-invasive diagnostic test for detection of breast cancer in those with an abnormal mammogram, etc. We present the data for these particular tests and also present this as a method for assessment of patient acceptability along side of an evaluation study of new diagnostic technologies.

METHODS

Study sample

We prospectively enrolled a cohort of white and African-American women, from several DC-metropolitan area clinics, hospitals, and HMOs, who have abnormal breast physical examination, mammography, and/or standard sonography results and have been recommended to have a breast biopsy. After signing the consent form, participants received a series of breast

cancer diagnostic tests, including digital mammography, magnetic resonance imaging (Gd-DTPA enhanced MRI), and nuclear medicine evaluation (Tc-99m-sestamibi scanning), during the one-day clinic visit. A short self-administered questionnaire about satisfaction and acceptability of the tests was given to women by the project coordinator after completion of all tests.

Measures

Patient characteristics included age, monthly household income, previous breast biopsy, history of benign breast disease, history of breast cancer, family history of breast cancer, and women's perceived chance of getting breast cancer in the future.

Satisfaction with participating in this study and with the overall experience of receiving the diagnostic tests was measured using a modification of the Medical Outcomes Study Visit Rating Questionnaire (Rubin et al, 1993). The six satisfaction questions measured satisfaction with the receipt of the tests overall, the technical skills of the staff, the personal manner of the staff, the convenience of getting the tests, the length of time spent waiting for the tests, and the explanation of what was done for the participants. Each question was measured by a five-item Likert scale, namely, "excellent," "very good," "Good," "Fair," and "Poor."

Discomfort associated with having a routine mammogram was measured using a 5-item Likert scale (extremely, very, somewhat, mildly, and not uncomfortable at all). To provide a relative standard, we asked the participants to rate discomfort of other tests compared to having a routine mammogram (a lot less, a little less, no different, a little more, a lot more). Embarrassment was measured using a 4-item Likert scale (extremely, somewhat, mildly, and not embarrassing at all) for all tests.

The willingness to pay (WTP) technique was used to assess women's preferences for having one of the diagnostic tests compared to a surgical biopsy. The WTP questions ask respondents how much money they think women like themselves would be willing to pay out-of-pocket for an alternative non-invasive diagnostic test instead of a biopsy. We have chosen to word these questions in the third person, based on prior experience in utility assessment among women with high risk of breast cancer (Lawrence, unpublished data). Two WTP scenarios were used to evaluate the impact of diagnostic accuracy on preferences. The first asks about willingness to pay to have a test instead of a biopsy, if the test were as accurate as a biopsy at diagnosing cancer; and the second asks about WTP if the test were nearly (95%) as accurate as a biopsy. We asked participants to imagine whichever test they would most prefer having, to avoid the respondent burden of asking about each test separately. Thus, the assessment provides the maximum the respondent would be willing to pay for any of the tests.

Data analysis

Analyses were performed using the SAS System version 8. Patient satisfaction, discomfort, and embarrassment scales were analyzed by frequencies and the non-parametric Kruskal-Wallis tests for difference in distribution. The differences in WTP by patient characteristics were presented by the average amount of money women would be willing to pay in individual scenarios and the ratio of the two scenarios using t tests and ANOVA tests. Since the WTP technique is sensitive to economic status, WTP was further defined as the amount a woman thinks women like her would be willing to pay as a proportion of the respondent's household income. Because of the small sample size and non-normal distribution of the ratio between WTP and income, the non-parametric Kruskal-Wallis test was used to test the difference in WTP by patient characteristics. Finally, the difference in the ratio between the two WTP

values (95% vs. 100% accuracy) by patient characteristics was analyzed using the non-parametric sign test.

RESULTS

Participant characteristics

A total of 106 patients were recruited for this study, 82 (77%) of which completed the acceptability survey. Those who completed and did not completed the survey were similar with respect to demographics (age, race, income, previous biopsy, history of benign breast disease or breast cancer, and family history of breast cancer). Results were discussed based on the 82 women completing the survey. The mean age of this sample was 51.6 (S.D.=10.2, range=25-78), 14%, 32%, 37%, and 11% of them were in the younger than 40, 41-49, 50-59, and 60 and older age groups. Eighty percent were white, and 14% were African Americans. About 23% had a monthly household income of up to \$3,000, and 13% and 64% had an income level of \$3,000 - \$4,999 and \$5,000 and above, respectively. Prior to entry into this study, about 46% (N=37) of them had a history of breast biopsy; 17 had benign breast disease; 1 had atypical hyperplasia, 2 was diagnosed with ductal carcinoma in situ (DCIS); 1 had lobular carcinoma in situ (LCIS); 9 had breast cancer. Thirty-six participants had a family history of breast cancer, and 2 had a family history of ovarian cancer. Of the 17 women with a benign breast disease, 7 did not receive a breast biopsy before the study. Finally, 41% (N=15) of those who reported having breast biopsy before (N=37) did not have benign or malignant breast disease.

Satisfaction with care

In general, participants were satisfied with the process of receiving different diagnostic tests (Table 1). About 96% of patients gave an excellent or very good rating of the overall process of participating in the study.

Acceptability—Degree of discomfort

About 20% of the participants reported that a routine mammogram made them very or extremely uncomfortable, and another 20% reported not uncomfortable at all (Figure 1). Among those receiving the tests, 47% of those receiving MRI, 50% of those receiving digital mammography, and 66% of those receiving sestamibi imaging found the procedure more comfortable than a routine mammogram (Table 2). Compared to routine mammography, nuclear medicine test was perceived as the most comfortable test.

Acceptability—Degree of embarrassment

Most of the participants did not feel embarrassed when receiving any of the diagnostic tests (Table 3).

Preference—Willingness to pay

Under conditions of equal accuracy to a biopsy, the 43 women who provided a response were willing to pay an average of \$611 to have a non-invasive test instead of a biopsy (range \$0-\$10,000), with 7% of women not willing to pay any money out of pocket (Table 4). The willingness to pay significantly decreased to an average of \$308 in the case of 95% accuracy (range \$0-\$3,000), with 33% of women not willing to pay any money (sign test $p < 0.0001$). This decrease of WTP was consistent across patient characteristics.

Regarding the difference in WTP by patient characteristics, the only significant comparison was the difference between WTP for 100% and 95% accuracy tests between those who had and who did not have benign breast diseases. However, interesting non-significant trends were observed in several categories: Women ages 60 and older were less willing to pay out of their pockets for diagnostic tests. Those who had previous biopsy with benign results were willing to spend more for other tests; whereas those with biopsy results of positive cell

change would pay less for diagnostic tests other than biopsy. Women with breast cancer or family history of breast cancer were less willing to pay for other diagnostic tests.

DISCUSSION

This study demonstrated that new non-invasive breast cancer diagnostic tests (digital mammography, MRI, and sestamibi nuclear medicine) are generally acceptable to women who have abnormal breast findings to whom a breast biopsy is recommended. Routine mammogram is considered an uncomfortable test in 80% of the participants, but only one fifth of them consider it embarrassing. Women consider these three diagnostic tests more comfortable than routine mammogram. The degree of embarrassment from taking these tests are similar to that seen in routine mammogram. Prior research shows that discomfort associated with mammogram is a barrier to regular breast cancer screening among old women (Loeken et al., 1996; Keefe et al., 1994). These results suggest that decreasing women's physical discomfort while receiving breast cancer diagnostic tests be one of the most important objectives for the development of new technologies to detect breast cancer.

The acceptability of new diagnostic test is influenced by its accuracy. In our study, the importance of test accuracy is examined by women's willingness to pay for the test out of their own pocket. We use the WTP as a process utility, or a quantitative measure of preference that may be applied to the process of care in evaluating an abnormal mammogram or clinical breast examination. A decrease of 5% accuracy, from 100% to 95%, of the preferred test result in a 40% decrease of willingness to pay in our sample, and the sizable decrease is consistent across different age, biopsy history, breast disease, family history of breast cancer, and risk perception of getting breast cancer. It suggests that accuracy of diagnostic tests appears to be more important than the level of discomfort and embarrassment associated with a test.

Moreover, the willingness to pay measure for tests with the same accuracy rate shows a series of non-significant trends according to patient characteristics. For instance, women with previous benign breast disease are more willing to pay for new diagnostic tests than those with no benign breast disease do. Although how these benign breast diseases are detected and worked up is not available from our data, it is highly possible that breast biopsy is used to confirm the diagnosis. These women may, judging from their experience, be more acceptable to new technologies if these tests can offer confirmatory diagnosis like biopsy and avoid unnecessary surgical procedures. Similarly, women with a history of benign biopsy results are more willing to pay for new tests than women having abnormal breast biopsy results prior to participation are. Women with personal or family history of breast cancer are more likely to favor biopsy and less likely to pay for new tests. It is mirrored by our finding that women with high risk perception are not as willing as those with low risk perception to pay for new tests even the tests are as good as biopsy in diagnosing breast cancer.

It should be noted that the interpretation of this study is limited by several factors. First, the small sample size does not give us enough power to detect significant relationships and the relative importance of patient characteristics on willingness to pay. Second, women's understanding of each test may not be accurate enough, since about 50% of the sample considered digital mammography less uncomfortable than routine mammography when in fact their difference is in imaging not in patient-related procedures. Third, the ratio of WTP and income may not reflect the adjustment of income, because the average income in each income category is used as the denominator in the absence of actual monthly income.

Despite of the limitations, this study one of the first studies using a prospective cohort to assess the satisfaction and acceptability of new breast cancer diagnostic tests. We conclude that women

would find these tests acceptable, and would find the tests preferable to biopsy if they were equally accurate or nearly equally accurate at evaluating breast lesions as biopsy. The development of novel breast cancer screening and diagnostic tests should focus on women's acceptability in terms of comfort of the procedures and accuracy of the tests. Future research should examine the associations between disease history and risk perception and willingness to pay using a larger and diverse sample.

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Table 1 Patient satisfaction with the diagnostic process.

	Overall	Technical skills	Personal manner	Convenience	Time spent in waiting	Explanation
N	79	66	80	81	79	81
Excellent	73%	83%	89%	43%	62%	80%
Very good	23%	15%	9%	40%	28%	16%
Good	1%	1%	1%	14%	5%	4%
Fair	3%	1%	1%	2%	5%	0%
Poor	0%	0%	0%	1%	0%	0%

Table 2 Discomfort experienced from diagnostic tests compared to a routine mammogram.

Discomfort compared to routine mammogram (score)	MRI	Digital mammogram	Nuclear medicine
	55 (67%)	14 (17%)	71 (87%)
A lot less (2)	27%	14%	45%
A little less (1)	20%	36%	21%
No different (0)	15%	50%	13%
A little more (-1)	16%	--	18%
A lot more (-2)	22%	--	3%
Mean score	0.15	0.64	0.87

Table 3 Embarrassment experienced from diagnostic tests.

Embarrassment level	Routine mammogram	MRI	Digital mammogram	Nuclear medicine
N	80	53	14	72
Not embarrassing at all	76%	87%	93%	83%
Mildly embarrassing	11%	11%	7%	11%
Somewhat embarrassing	11%	0%	0%	4%
Extremely embarrassing	1%	2%	0%	1%

Note: Kruskal-Wallis tests showed no significant difference among routine mammogram, MRI, digital mammogram, and nuclear medicine.

Table 4 Willingness to pay according to accuracy of diagnostic tests, by patient characteristics.

	100% accuracy (A)	95% accuracy (B)	Ratio (B/A)
Overall mean†	\$611 (1462)	\$308 (561)	0.60 (0.48)
Range	\$0 – \$10,000	\$0 – \$3,000	0 - 1
Chance of getting breast cancer			
Much higher	\$439 (453)	\$268 (340)	0.60 (0.45)
A little higher	\$428 (475)	\$300 (509)	0.58 (0.45)
The same or less	\$1,245 (3090)	\$465 (909)	0.67 (0.37)
ANOVA test p value	0.37	0.70	0.87
Household monthly income			
< \$3,000	\$446 (519)	\$169 (223)	0.58 (0.49)
\$3,000 – \$4,999	\$775 (1037)	\$495 (636)	0.57 (0.37)
≥ \$5,000	\$698 (1774)	\$368 (651)	0.60 (0.43)
ANOVA test p value	0.92	0.59	0.99
Age			
Up to 40	\$371 (372)	\$292 (304)	0.72 (0.40)
41-49	\$411 (629)	\$304 (403)	0.71 (0.40)
50-59	\$962 (2142)	\$412 (768)	0.48 (0.43)
60 and older	\$220 (193)	\$58 (68)	0.62 (0.49)
ANOVA test p value	0.54	0.52	0.43
Previous biopsy			
Yes	\$777 (2086)	\$329 (682)	0.47 (0.43)
with normal results	\$443 (440)	\$261 (402)	0.60 (0.42)
with benign results	\$1714 (3660)	\$589 (1096)	0.33 (0.47)
with positive cell change*	\$183 (194)	\$116 (194)	0.46 (0.42)
No	\$ 476 (623)	\$293 (463)	0.69 (0.40)
t-test p value	0.52	0.83	0.09
Benign breast disease ‡			
Yes	\$1325 (2808)	\$523 (893)	0.45 (0.45)
No	\$379 (463)	\$238 (395)	0.65 (0.41)
t-test p value	0.27	0.31	0.17
Breast cancer			
Yes	\$267 (208)	\$200 (265)	0.50 (0.50)
No	\$633 (1056)	\$315 (576)	0.60 (0.43)
t-test p value	0.16	0.73	0.69
Family history of breast cancer			
Yes	\$436 (570)	\$236 (381)	0.53 (0.47)
No	\$778 (1975)	\$377 (693)	0.65 (0.39)
t-test p value	0.41	0.39	0.38

† The difference in the WTP-to-income ratio between 100% accuracy and 95% accuracy groups was significant (sign test, $p < 0.0001$).

* Including atypical hyperplasia, DCIS, LCIS, and malignancy.

‡ The difference in the WTP-to-income ratio between 100% accuracy and 95% accuracy groups was significant between those having and not having benign breast diseases (Kruskal-Wallis test, $p = 0.027$).

Communication between Physicians and Older Women with Localized Breast Cancer: Implications for Treatment and Patient Satisfaction

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Supported by Department of the Army Contract #17-96-C-6069, Agency for Healthcare Research and Quality Grant #HS08395, and Department of the Army Grant #17-94-J-4212.

Running head: Communication about breast cancer treatment

ABSTRACT

Purpose: To identify factors associated with patient-physician communication and to examine the impact of communication on patients' perception of having a treatment choice, actual treatment received, and satisfaction with care among older breast cancer patients.

Methods: Data were collected from 613 pairs of surgeons and their older (≥ 67 years) patients diagnosed with localized breast cancer. Measures of patients' self-reported communication included physician- and patient-initiated communication and the number of treatment options discussed. Logistic regression analyses were conducted to examine the relationships between communication and outcomes.

Results: Patients who reported that their surgeons mentioned more treatment options were 2.21 times (95% C.I.=1.62-3.01) more likely to report being given a treatment choice, and 1.33 times (1.02-1.73) more likely to get breast conserving surgery with radiation than other types of treatment. Surgeons who were trained in surgical oncology, or who treated a high volume of breast cancer patients ($\geq 75\%$ of practice), were more likely to initiate communication with patients (OR=1.62 [1.02-2.56] and OR= 1.68 [1.01-2.76], respectively). A high degree of physician-initiated communication, in turn, was associated with patients' perception of having a treatment choice (OR=2.46 [1.29-4.70]), and satisfaction with breast cancer care (OR=2.13 [1.17-3.85]) in the 3-6 months post-surgery.

Conclusions: Greater patient-physician communication was associated with a sense of choice, actual treatment, and satisfaction with care. Technical information and caring components of communication impacted outcomes differently. Thus, the quality of cancer care for older breast cancer patients may be improved through interventions that improve communication within the

physician-patient dyad.

Key words: Physician-patient communication, breast cancer treatment, decision-making, satisfaction, elderly

INTRODUCTION

There is a relative paucity of data on communication in oncology settings. The limited data on patient-physician communication that do exist suggest that communication can have important effects on cancer treatment and patient outcomes.¹⁻⁶ Examination of the effects of patient-physician communication on determinates of, and outcomes from, surgical treatment for localized breast cancer is especially important since both breast conserving surgery (BCS) with radiation therapy (RT) and mastectomy have equivalent survival.⁷⁻¹⁰ In such situations, presentation of adequate information, discussion of the alternatives, and elicitation of patient preferences is key to shared decision making.

Despite the increasing use of BCS over the past decade,¹¹ older breast cancer patients receive BCS less often than younger women.¹²⁻¹⁴ In addition, within older populations, RT is sometimes omitted after BCS.¹⁵⁻¹⁷ While many factors may explain these patterns of care,¹⁸⁻²⁴ it is possible that the quality of communication between older patients and their cancer physicians contributes to the observed treatment variability. That this may be the case is suggested by the results of a recent study of breast cancer treatment in older women. In that study, Silliman and colleagues found that discussion of treatment options with physicians increased the probability of an older woman receiving definitive breast cancer therapy.¹⁹

Using data from a cohort sample of older women (≥ 67 years) with early stage breast cancer and their breast surgeons, this study addresses four research questions: (1) What factors are associated with more communication between older breast cancer patients and their surgeons? (2) Does communication influence patients' perception of having a treatment choice? (3) Does communication affect the type of treatment received? and (4) Is greater communication

associated with higher post-treatment patient satisfaction? We hypothesized that women age 80 years or older would report receiving less information about treatment options, would ask fewer questions, and would perceive their physicians as less communicative than women age 67-69 years old. We also hypothesized that greater physician-patient communication would be associated with a greater likelihood of receiving BCS with RT, compared to other types of treatment, and with increased satisfaction with breast cancer care.

METHODS

Setting and Study Population

The data for this study were collected as part of the breast cancer OPTIONS (Outcomes and Preferences for Treatment in Older Women Nationwide Study) project.²⁵ Institutional Review Board approval for this research was obtained at all participating institutions and all participating physicians and patients provided informed consent.

Women age 67 years or older diagnosed with localized breast cancer (T_{1-2} , N_{0-1} , M_0) in 29 hospitals in 5 geographic regions (Massachusetts, Texas, Washington D.C., Western New York State, and New York City) between November 1, 1995 and September 30, 1997 were potentially eligible ($n=1932$). After excluding those who had non-primary or multi-centric breast cancer, had insufficient cancer stage information, lived in a nursing home, did not speak English, or were cognitively impaired, 1,377 women remained eligible. Physicians' consent was obtained to contact 1,159 (84%) of these eligible women. Of the 784 (68%) women who agreed to participate, 66 were found to be ineligible after the interviews, resulting in 718 women in the final patient sample.

Surgeons ($n=194$) for the 718 participants were contacted to complete a survey. A total of

138 (70%) surgeons returned the survey. Of these, there were 613 (85%) pairs of patients with matching surgeon data. The characteristics of women with matching surgeon data were not significantly different with respect to age, race, education, or treatment received than women whose surgeons did not complete a survey (data not shown).

Data collection

Data for this study were collected from three sources: patient interview, medical record abstraction, and physician survey. Patients were contacted 6-24 weeks after surgery to complete a face-to-face interview; telephone interviews were conducted if patients lived more than 100 miles from a study site. Seventy-two percent of the interviews were conducted in person. Clinical information including procedures, histology, and tumor staging data were obtained through standardized review of medical records. The self-administered mailed surgeon survey included questions about demographic characteristics, self-reported practice patterns, and attitudes towards patient participation in treatment decision-making.

Measures

Outcome variables

Outcome variables included the patient's perception of having a choice of treatment, actual treatment received, and satisfaction with care. Each woman's perception of having a treatment choice was measured by her response (yes/no) to the question: "Do you feel you were given a choice about the types of surgeries or radiation treatments?"

Actual local breast cancer treatment actually received was categorized as breast conservation with radiotherapy (BCSRT), breast conservation alone (BCS), or mastectomy (MST). Breast conservation included excisional biopsy (with no follow-up procedures),

lumpectomy, partial or segmental mastectomy, tylectomy, quadrantectomy, and wedge resection. Mastectomy included modified radical mastectomy and simple mastectomy.

Patients' overall satisfaction with breast cancer surgery and other treatment was assessed by a single item on a 5-point Likert type response scale ranging from "1=very satisfied" to "5=very dissatisfied." Since most (78.3%) of the participants selected "1=very satisfied," we dichotomized this variable into "very satisfied" versus all other responses.

Predictor variables

Because communication depends on interactions between two parties, we separated communication into two variables to evaluate the relative importance of each component. The component reflecting what the patient brought to the interaction consisted of two questions modified from the Perceived Involvement in Care Scale.²⁶ These two items measured patients' information-seeking: "I asked my surgeon to explain breast cancer treatments and/or procedure(s) to me in greater detail" and "I asked my surgeon a lot of questions about my breast cancer treatment options (Cronbach's $\alpha=0.73$)."

The second component of physician-patient communication measured patients' report of surgeons' information-seeking and caring: "My surgeon asked me about my worries about breast cancer" and "My surgeon encouraged me to give my opinions about my breast cancer (Cronbach's $\alpha=0.68$)."

Responses on all four items were rated on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree." Since scores on scales were not distributed normally, we categorized scores at the median. Thus, scores on each sub-scale were categorized into two levels--high (score 2-5) and low (score 6-10) communication.

The amount of information about local breast cancer treatment that patients reported

receiving from their surgeons or other breast cancer specialists was measured by responses to the items: “Of the doctors you saw, did any of them mention (either recommend or discuss) any of the following treatments as options for your care?” Patients were then asked if breast conserving surgery, mastectomy, lymph node dissection, or radiation after BCS were mentioned. We used the sum of the number of treatment options mentioned to measure patients' perception of knowledge transfer during medical visits (scores ranged from 0 to 4).

Surgeons' attitudes were measured using an eleven-item scale about surgeons' attitudes toward patient involvement in treatment decision making developed by Liberati and colleagues.²⁴ Each question was rated on a 5-point Likert scale, ranging from strongly agree to strongly disagree. The higher the summary score (which ranged from 5 to 55), the more favorable a physician's attitude toward patient participation. The internal consistency of the items in the Liberati scale was moderate (Cronbach's $\alpha=0.63$); the average score among the 138 surgeons was 39.7.

Controlling variables

Several sets of variables were considered as having the potential to mediate the association between communication and outcomes. These included patient sociodemographic status, clinical and regional factors, process of care variables, and surgeon characteristics. Patient sociodemographic factors included age (67-79 vs 80+), race (white/non-white), socioeconomic status (measured by education, income, insurance, and whether working for pay), social support (number of adults living together), and marital status. Patients' insurance status was categorized as having private supplemental insurance versus Medicare alone (or Medicare and Medicaid) and HMO membership versus none.

Clinical factors included comorbidity and cancer stage. Patients were asked about selected chronic conditions likely to affect treatment choices. Comorbidity was defined as the number of illnesses reported by the patient in the two months prior to breast cancer diagnosis. Stage was defined as stage I ($T_1N_0M_0$), IIa ($T_1N_1M_0$ or $T_2N_0M_0$), and IIb ($T_2N_1M_0$), according to pathological and/or clinical staging; 75% were pathologically staged. Treatment sites were categorized according to the 5 geographic regions: Massachusetts, Texas, Washington D.C., Western New York State, and New York City.

Two variables were related to the process of breast cancer care: The first one reflected whether the woman saw another surgeon or a radiation oncologist for breast cancer information after her diagnosis but prior to surgery. The second variable reflected a composite score based on a woman's response to two questions that asked "Was any other person with you when the surgeon talked to you about your treatment decisions before your surgery (yes/no)?" and, if the answer was "yes", "Did that person help you make your decision about treatment (yes/no)?" If both answers were "yes," the variable of "having other person(s) present to help make treatment decisions" was coded as "yes;" otherwise this was coded as "no."

Surgeon-related variables included length of time in practice (graduated before 1975 or after), gender, specialty training in surgical oncology (yes/no), volume of breast cancer patients (>75% of practice or not), and affiliation with a National Cancer Institute (NCI)- designated cancer center.

Data analysis

Chi-square and t-tests were used to assess differences in categorical and continuous variables. A series of logistic regressions were then used to (1) identify factors associated with

patient-surgeon communication; (2) evaluate how patient, surgeon, clinical, process of care, and communication factors influenced patients' perception of having a treatment choice; (3) evaluate the effect of communication and patients' perception of having a treatment choice on treatment received; and (4) assess the relative importance of communication, patients' perception of having a treatment choice, and actual treatment received on patient satisfaction after treatment. The C statistic, an index of rank correlation, was used to test model fit.²⁷

Treatment models examined the differences between receiving one type of treatment versus all other treatments. In addition, we compared BCSRT and BCS to understand the factors influencing receipt of radiation therapy after BCS.

Missing data were handled in two ways. First, for those variables with more than 3% (about 20 observations) of values missing (i.e., patient income, volume of breast cancer patients cared for by surgeons, and second opinions sought by patients prior to surgery), a "missing" category was to retain the maximal size in the sample for logistic regression analyses. Second, in the case of satisfaction, where, due to an administrative error, 20% of women were not asked this question, subjects were excluded from analysis. Comparison between those with missing satisfaction values and those with non-missing values showed no differences in terms of sociodemographic characteristics, cancer stage, and communication. However, those with missing values were more likely to be from Texas (43% versus 31%, $p=0.018$) than any other region.

RESULTS

Description of the sample

The women in the study were predominantly white, well educated, with small (stage I)

tumors (Table 1). There were no differences in surgeons' demographics, medical practice background, and attitude toward patient participation when comparing their patients who were 67-79 years old and those 80 years and older. However, patients in the older age group felt that they received less information about treatment options (mean number of treatment options discussed 2.9 vs 3.5, $p<0.001$), and were less likely to state that they were given a choice of breast cancer treatment (75% vs 85%, $p=0.01$). Women age 80 and older also reported initiating communication with their surgeons less frequently, and also perceived that their surgeons initiated communication with them less frequently than did women 67-79 years old ($p=0.002$ and $p=0.07$, respectively) than women ages 67-79 years. There was no difference in level of satisfaction with care by age (84% vs 77%) (Table 1).

What factors were associated with communication?

After controlling for patient, surgeon, and clinical factors, the bivariate associations between age and patient- and physician-initiated communication (Table 1) were no longer significant (Table 2). Women who were accompanied by other people who helped them make treatment decisions reported asking questions 2.14 times (95% C.I.=1.39-3.31) more often than women who were unaccompanied. Surgeon factors that were associated with a higher degree of surgeon-initiated communication included training in surgical oncology factors (OR=1.62 [1.02-2.56]), seeing a high volume of breast cancer patients (OR=1.68 [1.01-2.76]), and absence of an affiliation with a cancer center (OR=0.39 [0.22-0.70]), after controlling for covariates. Contrary to expectation, surgeons' attitudes toward patient participation and surgeon gender were not associated with surgeon-initiated communication. Women who reported having a greater number of treatment options discussed with them were more likely to report higher patient- and surgeon-

initiated communication (OR=1.79 [1.40-2.28] and 1.44 [1.27-2.07], respectively) than women reporting few options discussed, after considering other factors.

Did communication influence women's perception of having a choice of treatment?

Women who perceived having more surgeon-initiated communication and who reported receiving more treatment information were significantly more likely to report that they had a choice of breast cancer treatment (OR=2.46 [1.29-4.70] and 2.21 [1.62-3.01], respectively), after considering other factors (Table 3). Patient-initiated communication and surgeons' attitudes toward patient participation in the decision-making process were not associated with treatment choice.

Did communication influence types of breast cancer treatment received?

In bivariate analyses, we found that among those reporting that BCS, radiation therapy, and mastectomy were all discussed before surgery (63% of the sample), 56% received BCS with radiation therapy and only 11% received BCS alone. Results from logistic regression showed that women who reported receiving more information about treatment options were 2.07 (95% C.I.=1.40-3.08) and 1.33 (95% C.I.=1.02-1.73) times more likely to get BCSRT compared to BCS alone or other types of treatment, after controlling for patient, physician, and clinical factors (Table 4). However, whether or not a woman or her surgeon asked questions about care did not appear to influence the type of treatment she received.

Did communication influence patient satisfaction?

Women who reported that their surgeons initiated communication with them were 2.13 times (95% C.I.=1.17-3.85) more likely to be satisfied than women who reported lower surgeon-initiated communication (Table 5). No other surgeon factors were related to patient satisfaction.

Interestingly, despite reporting lower communication than women 67-79 years old, women 80 years or older were 2.40 times (95% C.I.=1.07-5.41) more likely to report being satisfied with breast cancer care than women 67-79 years old, controlling for covariates.

DISCUSSION

Our results indicate that the amount of information older breast cancer patients report receiving affects their perception of communication and having a treatment choice, and may impact the type of local treatment received. Specific surgeon-related factors, such as training in surgical oncology and volume of breast cancer patients, are predictive of surgeon-initiated communication, which, in turn, affects older women's perception of having treatment choices and satisfaction with breast cancer care.

Interestingly, different types of communication impacted outcomes differently. For example, the amount of treatment information and surgeon-initiated communication were both associated with perceptions of having a treatment choice, but had different impacts in treatment and satisfaction. Increased treatment information was associated with better patient- and surgeon-initiated communication and receipt of RT after BCS. In contrast, a woman's perception of her surgeon's interest in her concerns was associated with greater satisfaction with care. This phenomenon points to the importance of looking separately at the "information" and "caring" aspects of physician communication; the former emphasizes sharing treatment-related medical information, and the latter addresses patients' personal concerns and emotional needs.²⁸ This finding is consistent with previous studies demonstrating that giving patients biomedical information or showing competence does not predict patient satisfaction, while addressing patients' psychological and emotional needs does.^{29,30} Medical information, on the other hand,

appeared to empower the oldest old patients (age 80 years and older) to make decisions and to receive RT after BCS. It appears that fully discussing medical options with older patients in a caring manner may help improve women's decision-making and health outcomes.³¹

Among surgeon factors, those specifically related to cancer or breast cancer care, such as training in surgical oncology and the volume of breast cancer patients, were more highly associated with surgeon-initiated communication than were gender, duration of practice, or attitudes toward patient participation in the medical encounter. Knowledge and experience in oncology and breast cancer care may enhance the ability to communicate information with women facing breast cancer surgery. Surprisingly, surgeons who were affiliated with cancer centers were less likely to ask patients about their worries or encourage patients to share their opinions. These surgeons may have a high patient volume and a tight schedule that limit their time to ask questions. Data on average time spent per visit would be needed to confirm this idea. Our result of lack of gender effects on communication, type of treatment performed, or patient satisfaction is different from prior studies demonstrating that female doctors communicate with their patients better than male doctors,^{32,33} and that older women of female surgeons are more likely to receive definitive breast cancer treatment than women cared for by male surgeons.³⁴ It is possible that there were too few female surgeons (24%) in our sample to detect gender effects. Furthermore, selection biases could have produced these null effects. For instance, those male physicians who communicated better with patients might be more willing to participate in this study than average male physicians, which, in turn, lessened the gender difference in communication.

Among women receiving BCS, the odds of receiving RT after BCS increased as the

number of treatment options patients reported having been discussed with them increased. Interestingly, however, women who reported having a treatment choice were more likely to have had BCS alone than BCS with radiation. Since the number of options increased definitive treatment, physicians presenting more information about treatment may empower a woman to choose BCS with radiation therapy more effectively than merely making her feel she has a choice of treatment. Older women are often concerned about their ability to manage self-care needs when making treatment decisions, and, if given a choice, they may prefer a therapy that does not require additional procedures after initial treatment.³⁵ Since older patients are less likely to seek medical information than younger patients,³⁶ our findings suggest that physicians may need to play a more active role in raising older women's awareness of the advantages and disadvantages of various treatment options and helping them choose an appropriate treatment. Alternatively, since having others present at medical visits increased patient-initiated communication, older women could be encouraged to bring a family member or friend with them when getting treatment information.

Despite that fact that women age 80 and older received less intensive local treatment, they were more satisfied with care than women age 67-79 years. This may be a cohort effect where older patients were less likely to question, more likely to accept, and more likely to be satisfied with the treatment they had. If it is indeed a cohort effect, it is likely that the association between advancing age and satisfaction may disappear in the future. Alternatively, women 80 years or older may be more satisfied with, or actually prefer less treatment.

Several caveats should be considered in interpreting our results. First, the generalizability of our findings is limited by the fact that this was a predominantly white, middle to upper-middle

class sample. While our response rate of 68% is similar to that in other studies of older breast cancer patients,¹⁹ non-participants may have differed from participants in communication styles. While non-participants and participants were similar in age, race, and treatment (data not shown), we have no data to address this possibility. If anything we would expect participants to be better communicators than non-participants, so that any communication effects we detected are likely to under-estimate the true magnitude of effects.

Second, because of the cross-sectional nature of our study design, we cannot make causal inferences. For instance, it is possible that patients' perception of having a choice of treatment is the cause but not the result of their interactions with surgeons. Moreover, because of the retrospective nature of the data, patients' perception of communication with surgeons is not an unbiased measure of what actually happened during the medical encounter. To understand the sequence of physician-patient communication, we would need to obtain detailed information via observation of both surgeons and patients at the time of actual decision-making. This direct observation was not deemed feasible in our study because of concerns about patient burden. Third, our single item measure of satisfaction does not focus on specific domains of care, such as satisfaction with surgeons' competence, communication skills, patients' ability to make treatment decisions, and type of treatment received. The unidimensional nature of our measure may explain why satisfaction did not correlate with patients' perception of having a treatment choice and types of treatment they received. Future research will benefit from longitudinal study designs that directly examine patient-physician interactions, includes comprehensive measures of decision-making and satisfaction, and is grounded in an extensive conceptual framework that helps explain the empirical findings.

Despite the above limitations, our findings suggest that physician-patient communication plays an important role in breast cancer treatment and outcomes among older women. Physicians appear to be a major source of information that women used in treatment decision-making. The magnitude of the impact depends on the type of communication. Technical, task-oriented medical information seems to help patients make optimal decisions for treatment, while conversations addressing personal concerns appear to increase patient satisfaction with care. Older cancer patients may feel satisfied with care even though they are not given enough information to make ultimate treatment choices. In addition, quality of cancer care can be improved if physicians also provide emotional support to older breast cancer patients and try to understand patients' concerns and preferences during treatment decision-making. Since our data show that surgeons who were trained in surgical oncology asked patients questions more often than those who were not, continuing medical education focusing on breast cancer treatment could be an ideal opportunity to enhance physicians' communication skills. Over the coming decades, older women are projected to constitute a larger absolute proportion of new breast cancer cases and survivors.³⁷⁻³⁹ Thus, it is important to maximize communication within the older patient-physician dyad to ensure that treatment is consistent with older women's preferences, is clinically appropriate, and maximizes post-treatment outcomes.

ACKNOWLEDGMENTS

The authors would like to thank the women who shared their breast cancer stories with us, the surgeons for completing surveys, the OPTIONS support staff who made data collection possible, Mathematica Policy Research, Inc for data management and collection, the OPTIONS National Advisory Committee for helpful suggestions on the conduct of the project, Ms. Sandy Fournier for administrative support, and Mr. Charles Cox for manuscript preparation.

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Table 1 Description of the study sample.

Description	Overall	Age 67-79	Age ≥ 80
Sample size	613	487	126
Mean age	75	73	83
Race (%White)	88%	88%	88%
Education***			
Less than high school	17%	14%	29%
High school graduate	27%	28%	25%
Some college or technical school	31%	32%	27%
College graduate and above	25%	26%	19%
Monthly income (Mean)***	1,000~1,999	2,000~2,999	1,000~1,999
Marital status (% Married)***	44%	49%	25%
Living situation (% Living alone)***	57%	38%	59%
Employment (% employed)***	16%	18%	6%
Private insurance in addition to Medicare	82%	83%	80%
HMO coverage*	26%	27%	18%
Mean number of comorbid diseases	2.4	2.3	2.7
Stage of breast cancer I	81%	78%	78%
IIa	11.6%	18%	19%
IIb	7.4%	4%	3%
Other doctors sought before surgery	28%	28%	27%
Other people present to help make treatment decision	28%	27%	32%
Given a choice for breast cancer treatment**	83%	85%	75%
Communication			
Patient-initiated (Mean)**	5.1 ¹	4.9 ¹	5.9 ¹
Surgeon-initiated (Mean)*	5.5 ¹	5.3 ¹	6.2 ¹
Number of treatment options mentioned by doctors (Mean)***	3.4	3.5	2.9
Surgeon's attitude toward patient participation (Mean) ²	39.7	39.9	39.3
Treatment Received**			
Breast conservation surgery and radiotherapy (BCSRT)	51%	57%	29%

(Table 1 continued)

Breast conservation surgery alone (BCS)	15%	10%	33%
Mastectomy (MST)	34%	33%	38%
Satisfaction with care (% Very satisfied)	78%	77%	84%
Surgeon factors			
Years of practice (% graduated before 1975)	51%	51%	54%
Gender (% Male)	76%	76%	77%
Training in surgical oncology	36%	35%	40%
Breast cancer doctor ($\geq 75\%$ breast cancer patients)	39%	40%	32%
Affiliation with cancer center	29%	30%	25%
Geographic areas			
Massachusetts	24%	24%	24%
New York (Upstate)	19%	18%	21%
New York City	6%	6%	4%
District of Columbia	17%	17%	17%
Texas	34%	34%	33%

1 Sum score ranging from 2 (high degree of communication) to 10 (low degree of communication).

2 Sum score ranging from 5 (favorable attitude toward patient participation) to 55 (unfavorable attitude toward patient participation).

* $0.05 \geq p \text{ value} > 0.01$

** $0.01 \geq p \text{ value} > 0.001$

*** $0.001 \geq p \text{ value}$

Table 2 Predictors of patient self-reported surgeon-patient communication.¹

Predictor Variables	Communication	
	Patient-initiated OR (95% C.I.)	Surgeon-initiated OR (95% C.I.)
<i>Patient factors</i>		
Age 80 and over (vs age 67-79)	0.73 (0.44-1.20)	0.70 (0.42-1.17)
Other people present to help make treatment decision	2.14 (1.39-3.31)	1.30 (0.86-1.98)
<i>Surgeon factors</i>		
Gender (Male vs female)	0.96 (0.57-1.65)	0.83 (0.48-1.42)
Training in surgical oncology (Yes vs no)	0.98 (0.62-1.56)	1.62 (1.02-2.56)
≥75% practice is breast surgery (Yes vs no)	1.42 (0.85-2.38)	1.68 (1.01-2.76)
Affiliation with cancer center (Yes vs no)	1.10 (0.61-1.96)	0.39 (0.22-0.70)
<i>Communication</i>		
Number of treatment options mentioned by doctors ²	1.79 (1.40-2.28)	1.44 (1.27-2.07)
Surgeon's attitude toward patient participation ³	0.99 (0.96-1.02)	1.03 (1.00-1.07)
C STATISTIC	0.71	0.72

- 1 Logistic regression controlling for patient race, education, income, marital status, living situation, private health insurance, comorbidity, second opinion, surgeon's year after graduation, stage of breast cancer, and geographic area.
- 2 Per 1 point increase, ranging from 1 to 4.
- 3 Per 1 point increase of the sum score, ranging from 5 (favorable attitude toward patient participation) to 55 (unfavorable attitude toward patient participation).

Table 3 Significant predictors of patient's perception of having been given a choice of breast cancer treatment.¹

Predictor variables	Having a choice of treatment
	Yes vs No OR (95% C.I.)
<i>Communication</i>	
Patient-initiated communication	1.34 (0.72-2.49)
Surgeon-initiated communication	2.46 (1.29-4.70)
Number of treatment options mentioned by doctors ²	2.21 (1.62-3.01)
Surgeon's attitude toward patient participation ³	0.98 (0.93-1.04)
C STATISTIC	0.80

1 Logistic regression controlling for patient age, race, education, income, marital status, living situation, employment, private health insurance, comorbidity, second opinion, surgeon gender, year of after graduation, volume of breast cancer patients, surgical oncology training, affiliation with cancer center, geographic area, and stage of breast cancer.

2 Per 1 point increase, ranging from 1 to 4.

3 Per 1 point increase of the sum score, ranging from 5 (favorable attitude toward patient participation) to 55 (unfavorable attitude toward patient participation).

Table 4 Predictors of treatment received among older women with localized breast cancer.¹

Predictor variables	Breast cancer treatment, OR (95% C.I.)			
	BCS+RT vs other	BCS alone vs other	BCS+RT vs BCS alone	MST vs other
<i>Patient factors</i>				
Age (≥ 80 vs 67-79)	0.38 (0.22-0.67)	3.75 (2.05-6.85)	0.16 (0.08-0.34)	0.95 (0.55-1.63)
Having a choice of breast cancer treatment	0.63 (0.35-1.13)	2.38 (1.03-5.54)	0.22 (0.08-0.63)	0.94 (0.52-1.71)
<i>Surgeon factors</i>				
$\geq 75\%$ breast cancer patients	1.89 (1.10-3.24)	0.66 (0.31-1.42)	1.74 (0.75-4.05)	0.63 (0.36-1.10)
<i>Communication</i>				
Patient-initiated communication (High vs Low)	0.85 (0.54-1.32)	1.35 (0.74-2.50)	0.74 (0.36-1.53)	1.05 (0.67-1.66)
Surgeon-initiated communication (High vs Low)	0.88 (0.57-1.37)	0.66 (0.36-1.20)	1.57 (0.77-3.28)	1.41 (0.89-2.22)
Number of treatment options mentioned by doctors ²	1.33 (1.02-1.73)	0.65 (0.47-0.90)	2.07 (1.40-3.08)	1.02 (0.77-1.33)
Surgeon's attitude toward patient participation ³	0.98 (0.95-1.02)	1.02 (0.97-1.07)	0.97 (0.92-1.03)	1.02 (0.98-1.05)
C STATISTIC	0.75	0.79	0.83	0.74

- 1 Logistic regression controlling for patient race, education, income, marital status, living situation, employment, health insurance, comorbidity, others present to help make treatment decisions, surgeon gender, year after graduation, volume of breast cancer patients, surgical oncology training, affiliation with cancer center, geographic area, and stage of breast cancer.
- 2 Per 1 point increase, ranging from 1 to 4.
- 2 Per 1 point increase of the sum score, ranging from 5 (favorable attitude toward patient participation) to 55 (unfavorable attitude toward patient participation).

Table 5 Predictors of satisfaction with breast cancer care among older women with localized breast cancer (n=423 pairs).

Predictor variables	Satisfaction with breast cancer care, OR (95% CI)
<i>Patient age</i>	
80 and over vs 67-79	2.40 (1.07-5.41)
<i>Communication</i>	
Patient-initiated communication	0.79 (0.45-1.40)
Surgeon-initiated communication	2.13 (1.17-3.85)
Number of treatment options mentioned by doctors	0.99 (0.69-1.40)
Surgeons' attitude toward patient participation	1.01 (0.96-1.07)
<i>Treatment received</i>	
BCSRT vs BCS	1.62 (0.73-3.60)
MST vs BCS	1.02 (0.45-2.30)
C STATISTIC	0.74

* The satisfaction question was not asked of the first 150 patients enrolled due to administration error.

Logistic regression controlling for patient age, race, education, income, marital status, living situation, employment, health insurance, comorbidity, social support, surgeon gender, year after graduation, volume of breast cancer patients, surgical oncology training, affiliation with cancer center, geographic area, and stage of breast cancer.

COST-EFFECTIVENESS OF GENETIC COUNSELING AND TESTING FOR BRCA1 AND BRCA2 BREAST CANCER SUSCEPTIBILITY MUTATIONS FOR HIGH-RISK WOMEN

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Information obtained from BRCA1 and BRCA2 breast cancer susceptibility genetic counseling and testing may enable women to make more informed decisions about their medical management. While testing is accepted as a research tool, clinical trials have yet to be performed to test whether counseling and testing reduce cancer morbidity and mortality in high-risk women. We used decision analytic methods to estimate the costs and outcomes of such counseling and testing based upon available data.

A computer simulation model determined the costs and quality-adjusted life years (QALYs) of offering genetic counseling and BRCA1/2 testing to high risk women, compared to offering counseling only, and to routine medical care (i.e. no counseling or testing). The model simulated development of breast cancer, ovarian cancer, and competing mortality. Probabilities were estimated from the current literature. Mutation frequencies for the baseline analysis (15.5% BRCA1, 6.7% BRCA2) were determined from a study cohort of women at high-risk for carrying susceptibility mutations. Quality of life weights were determined by rating scale assessment for this cohort. Costs of cancer care were estimated from Surveillance, Epidemiology, and End-Results (SEER) -Medicare linked data (personal communication M. Brown, J. Warren, 1999), and costs of counseling and full gene sequencing were determined by cost-accounting. Costs and QALYs were discounted at rate of 3%. An incremental cost-effectiveness ratio (CER) of \$50,000/QALY or less was considered to be cost-effective.

Results for the baseline analysis for a 45 year-old woman without cancer are shown in the Table. The CER was sensitive to the prevalence of susceptibility mutations in the cohort; if the prevalence was half the baseline value, the CER was \$26,529/QALY. The cost-effectiveness improved dramatically if all women who tested positive received prophylactic mastectomy and oophorectomy; under these conditions, the CER was \$632/QALY.

Strategy	Cost	QALY	Incremental Cost	Incremental QALY	Incremental \$/QALY
Routine Care	\$4,580	20.038			
Counseling Only	\$4,870	20.127	\$290	0.089	\$3,251
Counseling and Testing	\$6,532	20.287	\$1,662	0.160	\$10,389

We conclude that genetic counseling and BRCA1/2 testing is cost-effective for women at high-risk of carrying a susceptibility mutation. Future work will focus on high-risk women with cancer, and on alternative testing strategies.

The U.S. Army Medical Research and Materiel Command under DAMD 17-96-C-6069 supported this work.

[Abstract 2491 - ASCO Program/Proceedings, 2000]

QUALITY OF LIFE IN A PHASE I TRIAL OF TNP-470 AND PACLITAXEL IN PATIENTS WITH ADVANCED CANCER.

Preserving quality of life is an important goal of cancer therapy. The purpose of this study was to determine the quality of life of patients with advanced, incurable tumors participating in a phase I trial of TNP-470 [T] and paclitaxel [P]. T was administered as a 4-hour iv. infusion on day 1; P was started on day 8 as a 1-hour iv infusion, immediately followed by T. Both drugs were administered together weekly for 3 weeks, followed by a 1 week break. Quality of life was measured using two instruments. The FACT-G is a non-site-specific cancer survey that measures physical well-being (PWB), functional well-being (FWB), social well being (SWB), emotional well being (EWB), relationship with doctor (RWD), and a summary score (worst-best score: 0-116). The Health Utilities Index (HUI) is a utility index that measures overall preference for a participant's current health (worst-best score: 0-1). Surveys were administered at baseline, 2 weeks, and monthly while on therapy. Twenty two patients were accrued: 8 men and 14 women, median age 52 (33-74). Primary tumor sites included breast (5), lung (5), ovary (3), cervix (2), other (7). Complete survey data were available for 18 participants. Baseline and average follow-up FACT-G summary and HUI scores are shown in the table; PWB ($p=.033$) and SWB ($p=.050$) were also lower on treatment compared to baseline. Subgroup analyses show lower FACT-G summary and HUI scores in those treated with higher doses (133-177 mg/m² T; 90-100 mg/m² P), but not in those treated with lower doses (88.5-133 T; 70-80 P). Participants of the trial underwent a small but significant decrease in quality of life on treatment compared to baseline. Future work will examine the impact on quality of life of this regimen compared to other chemotherapy regimens.

Overall Quality of Life Scores

	Baseline	Treatment	p-value
Summary	80.8	76.1	.052
HUI	0.76	0.69	.017

Feasibility of Mobile Cancer Screening and Prevention

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Prepared under contract for Cancer Research Foundation of America. Also supported in part by the Agency for Health Care Policy and Research grant # HS 08395 (Dr. Mandelblatt), National Cancer Institute grant # RO1-CA72908 (Drs. Mandelblatt, Lawrence, and Yabroff), grant # DAMD17-94-J-4212 from the Department of the Army, Breast Cancer Center Grant (Drs. Lawrence, Liang, Kerner, and Mandelblatt), National Cancer Institute grant # RO3-CA83338 and DAMD 17-97-1-7131 from the Department of the Army (Dr. O'Malley), and National Cancer Institute training grant # RO1-CA09314 (Dr. Yabroff).

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ABSTRACT

Background: Many urban areas have high cancer mortality rates coupled with large medically under-served populations. Strategies to improve outcomes in these areas include mobile screening, currently used for screening mammography.

Objectives: To describe the feasibility, measured by acceptability and costs, of an urban multiphasic (i.e. multiple cancers) screening van, rather than one that does mammography alone.

Methods: Feasibility was evaluated using a combination of a review of the published literature and key informant interviews in urban locales. Costs were estimated by resource use from urban mobile screening units, and decision analysis was used to estimate the costs per cancer detected for breast, cervix, colorectal, and prostate cancer screening.

Main Results: Assessments of the need for, and acceptability of, a multiphasic cancer-screening van varied by perspective of the informant and needs of their clients. Common concerns centered on the need for continuity of care and the availability of post-screening (diagnostic and treatment) services for under-insured mobile facility users. Since mammography vans are often limited in their capacity for multiple clinical examinations, a solution frequently suggested by interviewees was to bring a van to primary care clinics. Feasibility and costs of screening and diagnosis were most sensitive to 4 parameters: age (i.e., incidence and prevalence of disease), prior screening history, risk factors, and volume of simultaneous examinations. Mobile breast cancer screening yielded the highest numbers of cases detected 7 per 1,000 women screened, at a cost of \$20,100 per cancer diagnosed. Cervical cancer screening was the least costly at \$3,090 per case of neoplasia detected. Even with targeting to some insured populations, and maintaining a high volume, operation of mobile screening vans requires an on-going investment of about \$200,000 per year (exclusive of diagnostic and treatment costs).

Conclusions: Subsidized mobile screening facilities may have the potential to reduce cancer morbidity and mortality if they target "hard to reach" under-screened groups, maintain a high volume, coordinate with local primary care services, and build on a strong infrastructure for providing diagnostic and treatment services regardless of ability to pay. It is unclear whether the investment required will translate into a reasonable cost per year of life saved.

Key words: underserved, cancer/prevention and control

INTRODUCTION

During the past two decades, cancer prevention and control efforts have largely focused on increasing breast and cervical cancer screening utilization.¹ Despite these efforts, there are still individuals who have never received screening and many who do not receive regular cancer screening. In the United States, persons who do not receive regular cancer screening are more likely to be elderly,²⁻⁸ uninsured or under-insured,⁸⁻⁹ lack a usual source of care,¹⁰⁻¹² have lower levels of education or income,^{8,13-16} be non-White,^{10-11, 17-21} be non-native English speaking,²² or have low levels of literacy.^{10, 23-4}

When patients are asked why they do not receive screening, the most important reason cited is that their physicians never told them they needed to be screened.^{10-11, 25} Taking mammography as an example, women report that they are also concerned about inconvenience, discomfort, and trouble.^{23,26} Practical considerations, such as absence of, or large distances to, mammography facilities, are associated with lower rates of mammography screening²⁷⁻⁸ and later stages at diagnosis of breast cancer.²⁹

It has been hypothesized that subsidized screening through mobile vans may address some of the remaining access barriers to cancer screening. For example, convenient mammography van-based screening has been shown to increase rates of screening.³⁰⁻³¹ Extension of mobile units to include other cancer screening tests may improve rates of utilization of other tests, but more importantly, may insure that patients are compliant with multiple rather than a single screening test recommendations. However, the feasibility, acceptability, and costs of instituting a mobile screening program are largely unreported.³² To address this gap, we discuss the feasibility, and costs of such a multi-site mobile cancer screening facility using both existing and modeled data as well as a series of key informant interviews. This feasibility study focuses on three cancer screening tests for which there is good evidence of effectiveness (breast, cervical and colorectal).³³⁻³⁷ While there is a lack of evidence on the effectiveness of prostate cancer screening,³³⁻³⁷ the costs of including it in a van are provided because it is frequently requested by consumers and advocacy groups.

METHODS

This feasibility study has a qualitative component consisting of key informant interviews, and a quantitative component consisting of an analysis of costs per screening test. In addition, we briefly review the effectiveness of common cancer screening tests and the logistics of their use in a mobile multi-phasic screening facility. The information on logistics of mobile screening comes from a combination of published literature and the experience of two directors of urban mobile mammography units.

Key informant interviews: Respondents for the key informant interviews were identified from inclusive program rosters of mobile mammography van staff, providers and administrators and public health providers and administrators working in conjunction with the van from throughout the metropolitan D.C. and Tampa areas. A convenience sample was drawn from the rosters with the goal of obtaining a distribution of respondent perspectives similar to their representation on the inclusive list. (e.g. community organizations, neighborhood representatives, clinics, public health directors, etc.) The interview guide was developed by two of the investigators and consisted of semi-structured open-ended questions. The key informant interviews were conducted and analyzed according to accepted qualitative methodologies.³⁸ Interviews were conducted until saturation of themes occurred. The main concepts, themes and issues that arose during each interview were compiled on a contact summary sheet for each interview based on field notes. Upon completion of the 21 interviews, the main themes were summarized in tabular form and reviewed by two of the study team members.

Cost Analyses: Costs were estimated using an accounting of resource use including: cost of disposable equipment, cost of personnel time to perform the intervention, and cost of the van for the time needed to perform the intervention. Costs of each intervention were calculated from the following components: Materials for the procedures were calculated using an accounting of necessary materials (mammograms, CBE, DRE) or by using Medicare laboratory reimbursement

for providing the test (Pap, FOBT, PSA). Personnel costs are calculated by estimating the time necessary for personnel to provide the intervention, multiplied by the average hourly wage plus fringe rate. The yearly screening van operation costs were estimated from the Wolk (1992)³⁹ and allocated based upon the van time required to perform the intervention. All costs are in 1999 dollars. Costs of follow-up procedures are estimated using Medicare reimbursement for specific procedures, multiplied by the probability that an individual getting screened will require the procedure. Costs of performing mobile screening mammography are estimated from a mobile-unit program directed by one of the authors (JL). Decision analysis was used to estimate the costs per cancer diagnosed (all cancers) for breast, cervical, colorectal, and prostate cancer screening. For colon and cervical cancer screening, we additionally provide cost per significant (cancerous and pre-cancerous) lesion diagnosed.

In our model, costs are included for the patient-van encounter up to the point of giving a person a diagnosis. E.g. we expect about 10% of mammograms to have an abnormality,⁴⁰⁻⁴⁴ so we estimated a cost of diagnostic work-up (to rule in or rule out cancer) and applied 10% of the cost to each mammogram. Treatment costs were not included.

RESULTS

Key Informant Interviews

Table 1 summarizes the results of key informant interviews conducted with providers, program staff, and administrators about the feasibility and acceptability of the mammography van from the program perspective (n=21). (see Appendix for the interview questions). One finding that was common to all programs was that advanced promotion and scheduling was necessary to ensure a reasonable volume. In other settings, women have stated that mobile screening would be acceptable if there was advanced notice and assurance of privacy and quality.⁴⁵ Other key findings noted by programs were the need for a substantial on-going subsidy to maintain van operations, even when case-mix is targeted to screening a large portion of insured individuals, and the limitations of space to conduct multiple screening activities simultaneously.

Several additional views and themes emerged from these interviews; these perspectives and experiences with the van tended to correspond to the informant's role in the health care delivery system. Four groups of informants were identified after considering the similarities in responses: 1) non-medical community organizations that do not directly provide health care (e.g., community centers, grocery stores or spas, churches, and advocacy groups) who acted as liaisons between their organizations and the van; 2) specialized closed system institutional sites, such as senior and residential homes; 3) primary care health clinics or specialty medical clinics; and 4) clinical and administrative leaders of county and city-wide programs (e.g., health departments overseeing primary care sites and overarching screening programs).

In general, key informant interviewees from *non-medical community organizations* were very positive about the van's provision of both mammography and other cancer screening services. Most of the respondents in this category were lay people rather than health care personnel. All of these community organizations targeted both their surrounding neighborhoods and specific groups of people using that organization's services (e.g., churches, spas, Salvation Army).

The second group of interviewees came from *institutional sites that were closed systems*, such as senior homes. These sites were all in favor of the van because it was extremely convenient for them to do screening on site. Most of the members of these homes were insured and could obtain screening elsewhere, but chose to use the van because of convenience. In other research, convenience has been cited as a factor which can enhance the feasibility of mobile screening vans.⁴⁵

Key informant interviewees from the third group, *primary care and specialty health care clinics*, had mixed but mostly favorable feelings about the mammography van and about a possible multiphasic van. The common theme from all of these clinics, regardless of whether they were primary care or specialty clinics, were that partnerships between the clinics and the van were critical for the success of the screening program. All felt that continuity and coordination of the patient's medical care was enhanced if the van came directly on-site to the

clinic to do the mammography. In addition, clinics also felt that the expertise of their staff (e.g., language skills in multi-cultural communities) could facilitate the van's screening process if the van was on-site. Finally, in other settings, it has been reported that while vans enhance convenience, many women still prefer to have these services as part of a primary care visit.⁴⁵

Universally, administrative interviewees expressed concern that the mammography vans (and a potential multiphasic screening van) could duplicate existing free screening services in their various geographic areas. However, all felt that the van was beneficial in the sense that it was highly visible and served to increase awareness about mammography. Above and beyond this marketing function, most did not feel that the van added to the already numerous facilities and programs for screening of at-risk populations.

All four groups expressed concerns about access to timely diagnostic and treatment services, should an individual using the van be found to have an abnormal screening test. All were concerned that, without an infrastructure to provide these services to un- and under-insured individuals, the potential benefits of early detection might not be realized.

Logistical Considerations for Multiphasic Screening:

Breast Cancer Screening:

At present, the number of mobile screening facilities is very limited. For instance, only 2.4% of all US mammography facilities were identified as being mobile in 1992.⁴⁰ Providing mammography requires a dedicated mammography unit installed in the van, as well as a processor. Film and developing supplies are required. A mammography technician is needed to take the mammograms, and a radiologist needs to review the films within 24 hours. In a mobile setting, the radiologist may not have old films available for comparison, leading to a high proportion of preliminary readings, and the need to re-read films a second time. Clinical breast examinations (CBE) require a nurse practitioner and an examination room, as well as a changing area. Results must be conveyed to primary care providers and follow-up systems need to be developed to ensure that all patients with abnormal results receive timely diagnostic resolution.

Cervical Cancer Screening:

Providing Pap smear screening requires a person skilled in the technique of taking a Pap smear (e.g., nurse, physician assistant, or nurse practitioner). It also requires space for an examination table with stirrups in the mobile unit and a private changing area. Also required are either disposable or sterilized speculums, large cotton swabs, microscope slides, cytologic fixative, and cervical sampling swabs or brushes. Examination gloves and a sink for hand washing will be necessary for the clinician, and a mechanism for handling biologic waste is necessary. Follow-up mechanisms for informing patients of Pap smear results, with recommendations to patients for abnormal smears must also be in place.

Colorectal Cancer Screening:

Fecal occult blood test cards could be issued to patients with written instructions for use, requiring minimal personnel time and training. Patients need to follow a special diet to maximize specificity of testing (ie, minimize false positive results due to ingestion of red meat), and would be required to place stool on the cards, and mail them to screening program. These literacy and behavioral requirements may reduce compliance with screening. Once the cards are returned, a trained person needs to evaluate the slide for occult blood, and the results will need to be tracked to notify patients. Flexible sigmoidoscopy requires the possession of sigmoidoscopes, equipment for operating the scope, an area dedicated to washing the scopes, a waiting area with restrooms for patients who will receive enemas prior to the examination. A clinician skilled in sigmoidoscopy (nurse practitioner or physician) and an assistant are required to perform the procedure, which takes approximately 20 minutes. In addition, patients need approximately 30 minutes of preparation time for the necessary enemas. Flexible sigmoidoscopy is only likely to be feasible in a fixed, non-mobile dedicated room.

Prostate Screening:

The two major tests currently in use for screening for prostate cancer are the digital rectal examination (DRE) and the Prostate Specific Antigen (PSA) blood test. The DRE requires a trained clinician to perform the examination. The PSA test requires a phlebotomist. Also

needed are rubber gloves, lubricant (for the DRE), phlebotomy supplies (needles, vacuum containers for storage of blood for the PSA), a sink for the clinician to wash, and facilities for disposal of biologic waste. While the clinician can give the patient the results of the DRE on-site, a tracking system would be necessary for the PSA results, and the program would require a follow-up to relay the results to the patients and primary care providers.

Additional Considerations:

Considerations for other screening and preventive measures are provided within the context of adding the intervention in a mobile unit already set up for mammography. One key issue related to conducting examinations (e.g., blood drawing for PSA or Pap smears) in a van that is equipped with a mammography unit is that the other examinations cause van motion which can produce "motion artifacts" and interfere with mammography film quality (personal communication, J. Lynn, 1999).

Another logistical consideration is that the small space of a mobile unit may impair privacy for mixed-sex screening, if participants need to disrobe for the examination. Finally, if multiple clinical examinations are required, the clinician needs to have more extensive training than required if only one examination is performed. While some studies have used nurses for breast examinations, we assume that breast, cervical, and/or prostate examinations will require a nurse practitioner.⁴

Medicolegal and Ethical Issues

While an in-depth consideration of the medical-legal and ethical aspects of the screening program are beyond the scope of this analysis, two items deserve mention. First, any clinicians (including physician assistants, registered nurses, and nurse practitioners) performing physical examinations would need to have some form of liability insurance for malpractice, which may add to the costs of screening. Second, both from a legal and an ethical standpoint, the program should be responsible for covering the costs of a diagnostic work-up (and treatment) should a

screening test be abnormal in a patient who is un- or under-insured or cannot afford the costs of the diagnostic evaluation and treatment services.

Effectiveness of Screening Interventions:

Breast Cancer: Currently, based on controlled trials, mammography and clinical breast examination are recommended for women ages 50 to 74 years of age³³. Regular screening is thought to reduce population mortality by 30%,⁴⁶ although this result has been recently challenged.⁴⁷ The American Cancer Society (ACS)⁴⁸ also recommends biannual or annual screening for women 40 to 49 years (1988), but the National Cancer Institute (NCI)³⁴ leaves this decision to the woman and her provider (1992), since the evidence that mammography reduces mortality in this age group is still uncertain,⁴⁹⁻⁵¹ and the costs are likely to be fairly high per year of life saved.⁵² We assumed that 2-view mammographic screening and clinical breast exam (CBE) would be performed in any multiphasic screening van for women ages 50 to 69 or 74 years.^{33-4, 46, 48-49, 53-54} We assumed CBE would be done on women under age 50 as well.

Current screening literature^{40, 41-44} suggests that about 10% of screening mammograms will be abnormal and require some sort of follow-up procedure, ranging from additional mammographic views to breast biopsy. Approximately 1-3% of the mammograms performed will result in a biopsy recommendation.

Cervical Cancer: While professional organizations agree on the effectiveness⁵⁵⁻⁵⁷ of Pap smear screening, the frequency of screening and the upper age-limit for cessation remain matters of debate.^{33-36, 48} All groups recommend initiation of screening at the start of sexual activity or age 18, with either annual or triennial smears following two annual negative results, until age 65;³³ the NCI or ACS do not impose an upper age limit; the Canadian Task Force recently raised their age limit to age 69;^{35,37} and, Medicare covers triennial Pap smears⁵⁸ with no upper age limit. Given the effectiveness of screening, the high proportion of minority women in the DC population, and the reasonable cost,⁵⁹⁻⁶¹ we assessed incorporation of cervical cancer screening of women ages 18 to 69 with an intact cervix into a mobile multi-phasic screening unit.

Approximately 8% of women will have an abnormal pap smear requiring evaluation, although this rate may be highly variable across settings and populations.^{59,62-4} Evaluation may include repeat Pap smears, or colposcopy and biopsy of the cervix. The majority of cervical abnormalities detected by Pap smear screening will be cervical dysplasias, including low-grade squamous intra epithelial lesions (LSILs, approximately 1-4% of results) and high-grade squamous intra-epithelial lesions (HSILs, approximately 0.3-1% of results),⁶⁵⁻⁶⁷ which may over time progress to invasive cervical cancer. Typically, if these lesions are diagnosed, they are treated by local destruction or excision of the dysplastic tissue, with close clinical follow-up. Controversy exists about management of an "atypical squamous cells of uncertain significance" (ASCUS) result on pap smear (approximately 3-5% of results). While some guidelines recommend frequent Pap smears for follow-up, some clinicians recommend colposcopy examination for women with this Pap smear finding.⁶⁸⁻⁶⁹ Cancer rates vary by age, but for women in the 55-59 year age group, we would expect 3 invasive cancers found per 1,000 women screened.⁷⁰

Colorectal Cancer: . To date, several randomized clinical screening trials using fecal occult blood testing have shown a reduction in colon cancer mortality of 15-35%.⁷¹⁻⁷³ A case-control study also showed that having a flexible sigmoidoscopy was associated with a lower risk of colon cancer mortality.⁷⁴ Screening with triennial sigmoidoscopy and/or annual stool guaiac cards is currently recommended by several professional groups.^{33, 75} Colonoscopy has also been advocated as a routine screening mechanism.⁷⁶⁻⁷⁷ While colonoscopy can be safely performed every three to five, or perhaps, ten years, this remains an expensive mode of screening.^{73, 78}

Given the logistical burden of performing colonoscopy or sigmoidoscopy on a mobile unit, and the effectiveness of FOBT screening,^{33, 71-74} we evaluated incorporation of FOBT alone into a multiphasic screening unit. This approach has the advantage of including both men and women in the screening program, and of being a reasonably easy screening test for the screening unit personnel to administer. The primary disadvantage of the screening is that the positive test rate is high, and follow-up diagnostic procedures are expensive. However, cost-effectiveness analyses suggest that the mortality and morbidity reductions from FOBT colorectal cancer screening are worth the cost,⁷⁹⁻⁸⁰ although the impact of burden of comorbid illness associated with advancing age on screening effectiveness has not yet been fully investigated.⁷⁷ Additionally, if a mobile facility could be brought to a community clinic with examination rooms set-up for sigmoidoscopy, this may be an attractive additional service, especially if nurse practitioners can be reimbursed for this service and back-up facilities are available to handle emergency complications (e.g., bowel perforations).

Approximately 7% of FOBT screens will be positive (range 2-11%) without rehydration of slides.⁸²⁻⁸⁸ Recommended follow-up for a positive FOBT includes either a colonoscopy or the combination of an air-contrast barium enema and flexible sigmoidoscopy.⁸⁹⁻⁹⁰ Based upon the Minnesota Colon Cancer Control Study,⁷¹ we would expect that about 2% of those who have a positive test will have colon cancer, and about 29% will have a colon polyp.

Prostate Cancer: While tests are available to screen for prostate cancer, screening is controversial, even in high-risk populations, since clear mortality reductions have not been convincingly demonstrated.^{33, 48, 91-94} At present, there is no professional consensus about screening recommendations. For example, the American Cancer Society and the American Urological Association advocate screening beginning at age 50 years, and earlier for African-American men and men with risk factors,⁴⁸ but the US Preventive Services Task Force does not recommend screening.³³ The American College of Physicians also does not recommend routine screening, but states that patient preference should guide the screening decision.⁷⁵ Thus, at this time there is insufficient evidence to recommend for or against PSA or DRE screening for prostate cancer in a mobile screening unit. Logistically, if prostate screening is desired, we consider the PSA without the DRE, since the PSA can be performed without need of an exam room.

Prostate cancer rates and PSA levels are dependent on age.⁹⁵ Based upon reported screening of cohorts starting either at age 40 or 50,⁹⁶⁻⁹⁸ we would expect approximately 10.5% of the cohort to have a positive PSA test (defined as 4.0 ng/dL or higher). In one cohort,⁹⁷ this positivity rate varied from 3% for men age 50-59 to 19% in men aged 70-79. Follow-up of an abnormal DRE or PSA would require a urologist's examination, a transrectal ultrasound to look for masses in the prostate, and either a directed or series of blind prostate biopsies, dependent on whether or not a suspicious mass was located. Cohort studies have suggested that approximately 25-27% of men over age 50 with a positive PSA will have prostate cancer, with higher levels of PSA reflecting higher risk of prostate cancer.

Smoking Cessation: While all of the above preventive measures are directed at specific cancers, tobacco control deserves mention as a primary prevention measure for multiple cancers (and cardiovascular disease). Both counseling and pharmacologic interventions have been shown in randomized trials to increase smoking cessation rates.⁹⁹⁻¹⁰⁰ Based upon the evidence for effectiveness of smoking cessation efforts, and the cost-effectiveness of smoking cessation,¹⁰¹ we would recommend the identification of all smokers who have appointments with brief advice and literature about quitting.

COSTS OF SCREENING PER DETECTED CASE

This section describes the costs per van-diagnosed cancer for breast, cervical, colorectal, and prostate cancer, including data on rates of suspicious tests requiring follow-up and prevalence of disease, and costs associated with further evaluation and diagnosis (exclusive of treatment costs) (Table 2). For all screening tests listed below, the estimated costs per case detected will be affected by the age of the population screened, the volume of examinations conducted,⁵⁹ risks for disease, and prior screening history of the target population.

Breast Cancer: The cost of breast cancer screening was estimated from the current experience of the George Washington University Mammovan Project (personal communication, J. Lynn, 1999). These investigators have reported a cost per patient screened of \$129, including radiologists' charges for reading the mammogram, but not including follow-up of abnormal mammograms (See table 2). We estimate the cost of performing CBE in the van to be \$70, assuming that CBEs can only be performed when the mammography unit is not operating; costs would be lower if simultaneous procedures can be conducted. Follow-up diagnostic costs for abnormal mammograms will add \$10 per person to the total mammography costs. This was calculated by using the probability of particular follow-up procedures being performed,⁴⁰ multiplied by the estimated cost of the procedure based on Medicare reimbursement (1999). This does not include cost of therapy.) Based upon screening cohort studies, we expect to find approximately 7 cancers per 1,000 women screened with mammography, at a cost per cancer diagnosed of \$20,100 per cancer.

Cervical Cancer: The cost of Pap screening is estimated at \$79 per woman for screening, and an additional \$6 per woman for follow-up testing of abnormal results (Table 2). (This assumes 8% of smears will be abnormal and that 90% of these women will have colposcopy and 10% will have colposcopy plus biopsy.) The cost per cancer diagnosed is estimated at \$35,400. While this figure is higher for that of breast cancer, it is somewhat misleading. If one includes HSIL and LSIL pre-invasive lesions in the number of significant abnormalities detected in addition to invasive cancer, then the cost per lesion detected drops to \$3,100.

Colorectal Cancer: The cost of screening with FOBT is estimated at \$35. We expect an additional cost of \$24 per person for follow-up of abnormal tests (Table 2). The cost per cancer

detected is estimated to be \$26,700, although if adenomatous polyps are considered with the invasive cancer, then the cost per lesion diagnosed becomes \$7,200.

Prostate Cancer: The cost of PSA testing is estimated at \$84 per person, with another \$26 per person expected for follow-up diagnostic testing of abnormal screening tests. The cost of DRE is estimated at \$70 (Table 2). The cost per cancer diagnosed is estimated to be \$3,800; this cost may be highly dependent on the age of the cohort screened. While the cost per prostate cancer diagnosed seems low, screening is controversial even in high-risk populations, since clear mortality reductions have not been convincingly demonstrated.^{33, 91-94} Thus, at this time there is insufficient evidence to recommend for or against PSA or DRE screening for prostate cancer in a mobile screening unit.

Smoking Cessation: Two levels of smoking cessation counseling could be implemented in a mobile screening unit. First, consistent with the AHCPR "smoking as a vital sign" cessation guideline, all smokers attending the unit could be identified on intake into the screening unit, and could be advised to quit. This advice could be 1-2 minutes in duration, with the patient referred to their own health care provider should they wish advice. The incremental cost of identification and very brief advice to smokers is minimal, as it can be done in the course of a routine screening visit. Second, if offering more intensive cessation counseling is desired, then a system of counseling appointments with a trained cessation counselor could be offered to smoking patients. It would be possible to conduct the counseling in an available room at the screening site, so that this service could be conducted simultaneously with other preventive services. Nicotine replacement therapy (NRT) by polacrilex gum or by transdermal patch could be recommended, but doesn't need to be a cost to the program since they are available without prescription. If the program does not pay for the NRT, however, it will be an out-of-pocket

expense for those smokers pursuing this option. The cost for the second form of counseling is estimated to be \$68 per person, for one session. If follow-up sessions are desired, or if NRT is distributed free of charge with the counseling session, then costs will increase.

Multiphasic Screening--Sensitivity Analyses

The cost per cancer (or lesion) diagnosed is sensitive to prevalence of disease and to the cost of the van time necessary for screening. If the prevalence of a particular disease being screened is double that of the baseline analyses, then the cost per cancer diagnosed will decrease by approximately half. Thus, the cost per cancer diagnosed will decrease when screening in high prevalence subgroups of the general population.

The cost per cancer diagnosed is also sensitive to the cost of operating the van. The baseline analysis assumes that one screening test is performed at a time, so that the entire cost of the van for that time is allocated to the one test. If the van is configured such that multiple interventions can occur simultaneously (e.g. mammography and pap smears), then the cost of the van for the time spent performing the interventions can be allocated across these interventions. For example, if two screening tests are performed simultaneously, then the van cost for each screening is one-half of baseline. For breast, cervical, and prostate, cancer testing, the contribution of the van towards the total cost of a screening test would decrease by \$25. This would drop the cost per cancer diagnosed to those shown in Table 3. As more activities can be performed simultaneously, the cost per cancer diagnosed will continue to decrease.

DISCUSSION

This feasibility study explored the perceptions of mobile unit providers and community-based van coordinators toward the extension of breast cancer screening vans to incorporate screening and preventive counseling for other types of cancers. It also estimated the costs per cancer diagnosed for an urban multi-phasic screening unit based on the best available data. The effectiveness of mobile screening in incrementally increasing already high screening rates and decreasing cancer morbidity and mortality will be a function of the: 1.) age and risk of the population targeted, the baseline rate of use of early detection services, 2.) response rates to invitations to be screened, 3.) volume of examinations, 4.) ability to screen for multiple cancers simultaneously, 5.) likelihood that clients obtain regular on-going screening at recommended intervals, and 6.) ability to promptly diagnose (and treat) clients who have abnormal screening tests (and cancerous or pre-cancerous conditions).¹⁰²

Unfortunately, in some mobile screening settings, low risk women have been the predominant users of services. For instance, Flynn and colleagues¹⁰³ found that only one-third of mobile mammography users were 50 years or older, despite this age group having the overwhelming majority of cancers detected; and in other programs mobile van users have been found to be significantly more likely to be prior users of screening than non-users or the general population.¹⁰⁴⁻¹⁰⁵ For most mobile programs, despite reasonable cancer detection rates^{32, 106} the operation requires an investment of more than \$200,000 per year (exclusive of diagnostic follow-up and treatment costs)³⁹ (personal communications K. Hall and J. Lynn 1999), and may not be as cost-efficient as stationary on-site screening programs.¹⁰⁷ In one national survey, however, 47% of mobile sites reported that they were financially profitable or were breaking even.¹⁰⁸

Another important barrier to use of mobile services is the resistance of the established medical community,¹⁰⁵ and the potential disruption of primary care.¹² Partnerships between a mobile facility and existing community primary care resources would address many of the issues surrounding feasibility, acceptability, continuity of care, efficiency, and minimization of

duplication of resources. Finally, screened women who have cancer but who do not receive prompt follow-up and adequate treatment, will not realize the benefits of early detection. For instance, in one mobile van program 38%-56% of women did not receive follow-up after a mammogram; rates of follow-up depended on severity of the reading, with women having films read as suspicious for cancer having the highest rate of follow-up.¹⁰⁹

An additional preventive intervention, dietary counseling, merits discussion here. Following cigarette smoking, diet is one of the most important behavioral factors associated with cancer risk. Diet has been reported to play a role in the development of esophageal, stomach, liver, lung, breast, prostate, and colorectal cancers,¹¹⁰⁻¹¹² and has been estimated to be responsible for as many as 35% of cancers diagnosed.¹¹³ Studies have demonstrated the feasibility of diet modification and the effectiveness of interventions in increasing fiber intake;¹¹⁴ trials of interventions to increase consumption of fruits and vegetables are currently underway.¹¹⁵ Dietary counseling appears to be acceptable to patients, provides a means to modify diet, and also has other positive health effects.¹¹⁶ However, to our knowledge, no studies have reported the costs, or cost-effectiveness of dietary modification in relation to cancer incidence or related outcomes. This is an important area for additional research. At present, if health educator staff is available, dietary counseling could be provided, perhaps along with smoking cessation advice for smokers. At a minimum, pamphlets about dietary guidelines could be distributed.

While we have estimated intermediate outcomes of costs per screening test and cost per cancer diagnosed in a mobile setting, it is difficult to translate these data into the "true" cost-effectiveness in terms of cost per year of life saved or cost per quality-adjusted year of life saved. This stems from two major issues: 1) difficulties in determining the incremental additive benefits (and costs) of targeting prevention and screening for multiple cancer sites; and 2) the "true" effectiveness of operating a mobile screening unit in a community within the framework of existing resources. For example, if a person obtains a screening test in the mobile unit that due

to access barriers would not otherwise be obtained, then the person may gain a longevity or quality of life benefit from the screening. If, on the other hand, the person would otherwise have been screened, but due to lower cost, easier access, greater convenience, etc., decided to obtain the screen from the mobile unit, then the person has received no additional health benefit from the addition of the mobile unit (although they may receive a financial benefit through avoidance of out-of-pocket costs).

Overall, subsidized mobile screening facilities may have some potential to reduce cancer morbidity and mortality. To realize this potential, such mobile units would need to target “hard to reach” un- and under-screened groups in the age and risk groups where disease is most likely to exist or develop, maintain a high volume, coordinate with local primary care services to maintain continuity of care and not duplicate existing resources, and build on a strong infrastructure for providing diagnostic and treatment services regardless of client ability to pay. At this time, it is unclear whether the investment required will translate into a reasonable cost per year of life saved. Ultimate decisions about resource allocation will depend on regional health care needs and priorities.

ACKNOWLEDGMENTS

The authors thank Kelly Hall of the L. Moffitt Cancer Center and the respondents for their time and thoughtfulness in providing data for key informant interviews. The authors also thank Ms. Kathy Summers, Ms. Christiana Hodge and Mr. Michael Burdick for assistance with report preparation.

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**Table 1. Key Informant Interviews with van staff, program administrators and providers:
Summary of key issues by groups of respondents.**

Number of Respondents:	Community Organizations	Primary Care or Specialty Health Care Clinics	System-Wide Players with a Global Perspective	Residential Institutions
	7	7	5	2
Perspective	Advocate for their clients	Provide general health care to their communities	Provide cancer screening and health care to their large areas	Address the specific needs of their residents
Overall Knowledge of health care system	Limited since almost none had health care experience; All focused on advocating for cancer screening	Good	Good	Limited to their populations
Socioeconomic Status of Clients	Mixed: Some middle class insured persons and some lower-income, uninsured persons	Mostly uninsured or underinsured lower income persons, many immigrants	Mostly uninsured or underinsured lower income persons	Insured older persons, Medicare
Positive Aspects of the Mammogram Van	Convenience Increases awareness	Convenience One-stop shopping. On-site services at clinic can maximize continuity and coordination of and optimize use of the clinic staff's expertise.	Highly Visible Increases awareness	Convenience For those institutions with on-site physicians, continuity of medical care is maintained.

Down-sides to Mammogram Van	No mechanism to ensure regular screening over time.	Follow-up and repeat screening is very difficult for transient populations or for persons who get screened on the van but then don't have anyone with whom they follow-up on a regular basis.	Duplication of Services. There are so many free screening programs already available. Need to focus more on why some are not getting screened, on streamlining screening and on coordinating screening to promote optimal primary care, regular screening over time, and good follow-up.	None
Feelings on a Multi-Phasic Cancer Screening Van	Good idea. Goal is to get the screening services as accessible as possible to our communities. Big interest in prostate screening for men.	Interesting idea Would be very important for it to act in partnership with the clinics, on-site. Would be extremely important for the van and the clinics to have each of their roles, responsibilities and expectations clearly outlined. It would be very important for any screening done to be coordinated with the person's general primary care to ensure adequate follow-up and regular screening in the future. "Who's going to pay for all of the follow-up care and treatment that gets generated from a multi-phasic van? We don't have resources for this."	May duplicate already existing services. Focus instead on maximizing peoples' use of existing screening services. Who will perform, coordinate and pay for all of the follow-up that gets generated by a multi-phasic van? Ideally the van would focus on reaching persons for whom other free screening programs don't already exist. (e.g., rural communities with no mammogram facilities and high proportions of uninsured persons).	Good idea Enhances access for our group for those screening tests which physicians don't do on-site

Table 2. Costs of Cancer Prevention and Screening Interventions

	BREAST		CERVICAL	COLON	PROSTATE		MISC
	Mammogram	CBE			DRE	PSA	
Screen Costs (materials)	\$63	\$1					
			Pap Smear	FOBT			Smoking Cessation
Personnel	\$16	\$19	\$8	\$5	\$1	\$29	\$0
Van	\$50	\$50	\$20	\$5	\$19	\$5	\$17
			\$50	\$25	\$50	\$50	\$50
Total	\$129	\$70	\$79	\$35	\$70	\$84	\$68
Screening							
Follow-up	\$10	--	\$6	\$24	--	\$26	\$0
Total	\$139	\$70	\$85	\$59	\$70	\$110	\$68

CBE = Clinical breast examination
 DRE = Digital rectal examination
 FOBT = Fecal occult blood testing
 Pap = Papanicolaou smear
 PSA = Prostatic specific antigen

Table 3. Cost per cancer diagnosed—Single vs. Multiphasic Screening Estimates

Intervention	Baseline cost/cancer	Cost/cancer – 2 simultaneous interventions
Mammography	\$20,121	\$16,439
Pap (cancer only)	\$35,409	\$24,916
Pap (cancer and pre-invasive lesions)	\$3,090	\$2,174
FOBT (cancer only)	\$26,688	\$20,965
FOBT (cancer and polyps)	\$7,160	\$5,625
PSA (prostate cancer)	\$3,803	\$2,935

(Note to editors/reviewers: Inclusion of this appendix is an option)

Appendix : Summary of Questions for Key Informant Interviews

- 1.) What has been your role with regard to the mobile mammography van that came to your clinic/site?
- 2.) Would you say that the mammovan provided a needed service to your community/clients/patients?
- 3a.) Has the mammovan benefited your community/clients/patients?
- 3b.) If yes, in what ways?
- 4a.) How would you characterize the members of your community/clients/patients in terms of their use of cancer screening services prior to the visit of the van?
- 4b.) Were they regular users of general medical (primary) care?
- 4c.) Were they women who have regular primary care doctors?
- 4d.) Were they people who had no source of care and would not have otherwise gotten a mammogram?
- 4e.) Do you know the screening history of those who used the van?
- 4f.) Are you reaching previously unscreened men and women, or those who have primary care and get regular exams anyway?
- 5.) What is your best estimate of the percentage of your clients/patients that fall into each of these categories:
 - 5a.) % of the people seen at your clinic who are regular users of your site: %
 - 5b.) % of the people seen at your clinic for whom your clinic is their main site of care: %
 - 5c.) % Having a regular primary care doctor at your site: %
 - 5d.) % of persons who have no other source of medical care outside of your clinic %
 - 5e.) % of persons who would not have otherwise gotten a mammogram %
- 6.) Do you think that the van enhances or disrupts patients' continuity with their regular health care providers?

- 7.) How would you characterize the socioeconomic status of your community/clients/patients who made appointments (for the van)?
- 8.) Who actually used the van?
- 9.) What % of appointments were kept?
- 10.) Can you estimate the proportion of your community/clients/patients who needed breast cancer screening that actually used the van?
- 11.) Have you gotten any feedback on the acceptability of, and satisfaction with the van from your community/clients/patients?
 - 11a.) What was positive?
 - 11b.) What was negative?
- 12.) What % of women from your clinic who had mammograms on the van had thorough and reliable follow-up of their test results?
- 13.) What % of the time did you hear about their results in a timely fashion?
- 14.) Was it hard or easy to coordinate communication with the van?
- 15.) Do you think that the van reaches a population that would not otherwise get mammograms at some of the other sites where free mammograms are already offered? (Like Columbia Hospital, and Project Wish)
- 16.) What down-sides (negative aspects) do you see to using a mammography van?
- 17.) How much time and effort and other resources do you need to expend to promote the van, schedule clients, etc?
- 18.) Can you put a dollar amount to these resources?
- 19.) If the van expanded services from providing breast cancer screening to include other cancer screening, (like cervical, colorectal etc.) do you think your community/clients/patients would use it?
- 20.) Would a van proving multi-phasic cancer screening (breast, cervix, colorectal, prostate, and skin) be a useful service for your community/clients/patients?
- 21.) Do you think women would use it?
- 22.) Do you think men would use it?

- 23.) Are men and women equally interested in participating?
- 24.) Do you think it would be feasible to form a partnership between a community clinic and a mobile van to enhance provision of cancer screening and follow-up services?
- 25.) What would you see as the barriers to such a partnership?
- 26.) Advantages of such a partnership?
- 27.) What other cancer screening services are available to your community/clients/patients now?
- 28.) Where?
- 29.) For which cancer sites?
- 30.) Can your community/clients/clinics handle an increased volume of need for diagnostic follow-up after an abnormal screening test or treatment of a detected cancer?
- 31.) Does your community/clients/patients have insurance or other coverage for these services?
- 32.) What advantages do you see to having a van that does other cancer screening as well as mammography?
- 33.) What down-sides do you see to having a van that does other cancer screening as well as mammography?

FROM RESEARCH TO PRACTICE

Assessing the Effectiveness of Health Interventions for Cost-Effectiveness Analysis

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Cost-effectiveness analysis (CEA) is an analytic tool in which the costs and effects of an intervention designed to prevent, diagnose, or treat disease are calculated and compared with an alternative strategy to achieve the same goals. The results of a CEA are presented as a ratio of costs to effects, where the effects are health outcomes such as cases of disease prevented, years of life gained, or quality-adjusted life years gained, rather than monetary measures, as in cost-benefit analysis. Conducting a CEA requires a framework for portraying the cascade of events that occur as a consequence of the decision to intervene, for describing the probability that each event will occur, for accounting how long each event will last, and describing how much each event costs and is valued by the population or individuals targeted by the intervention. Mathematical models are well suited to these purposes.

The purpose of this article is to provide an overview of modeling to estimate net effectiveness in a CEA (the difference in effectiveness between an intervention and the alternative to which it is being compared). Many of the principles described for estimating effectiveness apply equally to determining costs in a CEA. The main difference is that health events are weighted by costs in the numerator of the cost-effectiveness ratio, while they are often weighted by preference values in the denominator. Preference values, or utilities, reflect the fact that individuals or populations with similar ability (or disability) to function may regard that level of functioning differently. When preferences are incorporated into CEAs, the results are generally expressed as costs per quality-adjusted life years.^{1,2} A discussion of measurement of costs and valuing outcomes is beyond the scope of this article; for further information on these, and other components of a CEA, the reader is referred else-

where.³⁻⁵ Following some definitions of terms, this article is organized into two sections describing the process of estimating effectiveness in a CEA: the first presents a review of the sources of event probabilities, and the second describes the use of modeling to estimate effectiveness.

DEFINITIONS

Effectiveness, which reflects the impact of an intervention of health in real practice settings, should be distin-

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The Panel on Cost-Effectiveness in Health and Medicine was convened by the Office of Disease Prevention and Health Promotion. The work presented in this paper is the responsibility of the authors, and does not reflect the views of the U.S. Public Health Service.

Dr. Mandelblatt's work was supported, in part, by grant RO1 HS08395, "Care, Costs, and Outcomes of Breast Cancer in the Elderly," from the Agency for Health Care Policy and Research, and Contract DAMD17-96-C-6069, "Breast Cancer Center Support Contract," from the Department of the Army (the "Cancer Clinical and Economic Outcomes Core" is one of the projects funded by this contract).

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guished from two related concepts, efficacy and appropriateness. Efficacy refers to impact under ideal conditions (e.g., randomized controlled trials). Appropriateness reflects a broader range of issues considered in deciding whether an intervention should or should not be done, including acceptability, feasibility, and cost-effectiveness.⁶⁻⁸

Cost-effectiveness analysis calculates incremental effectiveness (and costs); that is, the difference in effectiveness (and costs) between the intervention of interest, and the next least effective (costly) alternative. This is distinguished from marginal effects (and costs), which refer to a production function, where, for instance there are other effects (or costs) associated with producing one additional unit of output.

To calculate *net* effectiveness, we must estimate the probabilities of all events that occur as a consequence of the intervention and alternative. Probabilities express the degree of certainty that an event will happen, on a scale from 0.0 (certainty that the event will not occur) to 1.0 (certainty that the event will occur). Probabilities found in the literature are often not in the form required for the CEA.⁹⁻¹⁴ For instance, a lifetime cumulative risk of breast cancer must be converted to an annual probability.

DATA SOURCES FOR PROBABILITY ESTIMATES

Cost-effectiveness analysis probability data can be collected as part of a research protocol (primary data), or can be abstracted or extrapolated from existing published research (secondary data). Event probability values should be selected or collected from the best designed and least biased sources that are relevant to the question and population under study using the following hierarchy (in decreasing order): well-conducted randomized, controlled trials (RCTs); observational data, including cohort, case-control, and cross-sectional studies; uncontrolled experiments; descriptive series; and expert opinion.¹⁵ Less rigorously designed studies drawing similar conclusions may be the best available source of data for a particular subpopulation or research hypothesis, in the absence of other data.

Table 1 summarizes the main advantages and disadvantages of different study designs as data sources for a CEA.¹⁶ Although well-conducted RCTs are generally accepted as the most powerful tool for assessing the efficacy of interventions, in CEA one is most interested in how an intervention performs in real-life (i.e., non-RCT) settings. Observational cohort and case-control studies can provide real-world data on the probabilities of particular outcomes associated with an intervention. Observational studies differ from RCTs in that the investigators do not have control over which persons receive the intervention, so that observational studies may be subject to unknown selection effects. Also, the use of case-control studies to evaluate the effectiveness of screening can be biased by the type of case or control group selected.¹⁷⁻²¹

For example, in evaluating the effectiveness of sigmoidoscopy screening to reduce mortality from colorectal cancer, cases should include all those dying from the dis-

ease, and controls should include both those with colorectal cancer who are still alive and those without cancer. Moreover, the definition of cancers in both the case and control groups should include those in reach of the sigmoidoscope and those beyond.²² This choice of study groups eliminates the lead time bias that would occur in situations if early-stage cases were compared with later-stage cases, where lead time bias is defined as resulting in earlier diagnosis, even though survival does not actually differ in screened and unscreened groups. Cross-sectional studies, case series, uncontrolled cohort studies, post-marketing surveillance, and disease and administrative databases may also provide data for a CEA.²³⁻²⁷

When there are insufficient data from any one source or when studies conflict, information from many types of good-quality studies can be combined to provide probability values for estimating effectiveness. The two major approaches are meta-analysis²⁸⁻³² and Bayesian methods.^{33,34} Expert opinion and consensus panels are other synthesis techniques used to estimate effectiveness. For example, the original Oregon priority list relied on educated guesses of experts who estimated the ability of particular technologies and practices to improve survival.³⁵ For further information on sources of effectiveness data, the reader is referred elsewhere.^{23,36,37}

MODELING TO ESTIMATE EFFECTIVENESS

Randomized control trials and observational studies cannot compare all relevant alternative program designs that may be of interest to the CEA analyst or policy maker. Models have the advantage of providing the user with the ability to manipulate an intervention program in ways that are not possible in real-time experiments with human subjects. Models can be used to extrapolate from existing data to different population groups, points in time, or disease end points. For instance, models enable exploration of the implications of different screening or treatment intervals. Models allow simulation of the effects and costs of ending a screening program at a given age, investigating questions such as whether to continue cervical screening past the sixth decade of life. Models allow examination of the implications of using different cutoff points for screening tests, such as the cholesterol level chosen for initiating dietary or pharmacologic intervention, or the bone mineral density level chosen for initiating treatment for osteoporosis. Models can also be of use in performing sensitivity analyses and threshold analyses to ask what the data parameters would need to be for an intervention to be considered cost-effective.³⁸

Types of Models

Models for estimating health effectiveness may be characterized along several dimensions: (1) the analytic methodology for accounting for events that occur over time, typically either a decision tree or state transition model; (2) application to cohorts longitudinally or to popu-

Table 1. Sources of Probability Data for Cost-Effectiveness Analysis

	Randomized Controlled Trials	Cohort Studies	Observational Studies and Case- Control Studies	Administrative Data	Synthesis Methods	Expert Opinion
Advantages	1. Randomization controls for known and unknown confounders 2. Outcome evaluation done without knowledge of study arm	1. Tests effectiveness 2. Potential for broad population inclusion	1. Tests effectiveness 2. Does not require long observation periods	1. May include data on large populations	1. Can address questions not previously posed 2. Increases power to detect effects 3. Improves precision estimates	1. Useful when few data exist
Disadvantages	1. Selection bias* 2. Usually tests efficacy 3. Limited periods of observation 4. Contamination effects†	1. Selection bias* 2. Can only control for known confounders 3. Requires long periods of follow-up	1. Selection bias* 2. Can only control for known confounders 3. Recall bias‡ 4. Difficulty in selection of proper control group	1. Limited types of data available 2. Incomplete data possible 3. Confidentiality issues	1. Quality depends on quality of original studies included 2. Publication bias§	1. Process for combining data is left to the judgment of the experts 2. Quasi-scientific 3. Subject to bias from cognitive heuristics

*Selection bias: healthy subjects may volunteer to participate in research; subjects participating in research (or surviving to participate) may differ on unmeasured characteristics from those who do not participate.

†Contamination effects: the limited window of opportunity to conduct a trial or study prior to widespread introduction of an intervention into clinical practice.

‡Recall bias: subjects with disease may be more likely to recall past exposures than subjects without disease.

§Publication bias: studies finding a positive intervention effect are more likely to be published than those finding a negative effect or no effect.

||Cognitive heuristics: simplistic judgment and memory processing strategies to formulate probability assessments.

lations cross-sectionally; and (3) using deterministic or stochastic (probabilistic) calculations.

Analytic Methodology

Decision tree models represent chance events and decisions over time.³⁹⁻⁴¹ Each path through the decision tree represents one possible sequence of events, and is associated with a probability and a consequence, such as life expectancy, or quality-adjusted life expectancy. Decision analysis models have been used extensively in the medical literature, for example, to estimate gains in life expectancy from vaccines,⁴²⁻⁴⁴ and for screening elderly women for breast cancer.⁴⁵ One limitation of decision trees is that they are not well suited to representing multiple outcome events that recur over time.

State-transition models are more efficient representations of recurring events. State-transition models allocate, and subsequently reallocate, members of a population into one of several categories, or *states*. States may be de-

finer according to disease stage, treatment status, or a combination of the two. Transitions occur from one state to another at defined, recurring time intervals (usually 1 year, but sometimes 3 months or 1 month for rapidly progressive diseases) according to transition probabilities. Transition probabilities can be made dependent on population characteristics, such as age or other risk factors.

Through simulation, or mathematical calculation, the number of members of the population passing through each state at each point in time can be estimated. A special type of state-transition model, in which the transition probabilities depend only on the current state (and not, for example, on the previous states or the path by which the current state was entered), is called a Markov model.⁴⁶ State-transition models have been used to estimate outcomes in a large number of cost-effectiveness studies, including coronary heart disease prevention⁴⁷ and treatment⁴⁸; breast,⁴⁹ cervical,⁵⁰ and prostate cancer screening⁵¹; and hormone replacement therapy.⁵² Decision tree models can also be augmented to include "Markov nodes," or

branching points within the tree that lead into a Markov model.⁵³ Several computer programs, such as SMLTREE (© 1989, J. Hollenberg), DATA (© 1994, TreeAge Software, Inc.), and Decision Maker (© 1980, 1993, S.G. Pauker, F.A. Sonnenberg, and J.B. Wong, New England Medical Center, Boston, Mass.) can be used to construct such models. Other types of models, such as difference equations, have been used to assess the effectiveness of interventions targeting infectious diseases, such as AIDS prevention programs.⁵⁴

Longitudinal and Cross-Sectional Models

All models include a population or group that is relevant to the research question. Simulations then project future outcomes or "follow the patients or individuals over time." There are two common ways these modeling approaches can be accomplished, differing in the way in which the study population is constituted at the start of the model.

The first method, known as *longitudinal modeling*, calculates expected outcomes for "typical" patients or cohorts (i.e., groups of 50-year-old men with a first myocardial infarction) and follows them longitudinally through time to evaluate health outcomes resulting from alternative interventions. This approach is often used in decision tree models or models to extend the follow-up period of an RCT from the end of the trial, typically 1 to 5 years, to death.⁵⁵ Results of such models are typically expressed as quality-adjusted life-years.

The second method is known as the *cross-sectional model*. These models record the health outcomes of a cross-section of an entire population, or a substrata of the population, and then follow each person in the population from their age at the start of the model to the end-point of the analysis (either a specified period, such as 10 years, or until death). The outcomes from alternative interventions are then summed or averaged over the population and expressed as an aggregate measure, such as quality-adjusted person-years. The model CAN*TROL and the Coronary Heart Disease Policy Model are examples of cross-sectional population models.^{47,56}

The choice of a cross-sectional or longitudinal model is determined by the problem being studied. For instance, a cross-sectional model may be used to ask public health questions about interventions that are to be applied population-wide to groups of varying ages; a longitudinal model may be used to ask questions about the long-term effects of an intervention on an age-specific group.

Deterministic and Stochastic Models

Deterministic models calculate probabilities as an average number of health events. For example, suppose that one is interested in the number of people in a cohort of 10,000 who will be dead in 10 years from a particular disease, and suppose further that one knows the annual disease-specific mortality rate is 10% and the average annual other-cause

mortality rate is 1%. The number of people who will be dead from the disease can be computed directly by multiplying the survival percentages by the expected number of survivors recursively in each of the 10 years.

In *stochastic models*, known as *discrete event simulations*, probabilities for each individual in the cohort over time are simulated using computer-generated random numbers to represent chance events. For instance, to calculate 10-year survival, simulating a 10% chance of death in a given year, the computer is directed to generate a random integer between 1 and 100, and if that integer is 10 or less, the computer program tallies the simulated person as dying in that year; otherwise, the person is deemed to have survived. The process is repeated over time for the survivors. The number of people in the cohort who are "observed" to live the full 10 years in the simulation is used as an estimate of the number that would be observed were a real study done under conditions of the simulation. The entire simulation is repeated many times, and the counts are averaged across simulation runs; as the number of runs grows large, these averages approach the values that would be computed by deterministic calculations. This type of discrete event simulation is also known as Monte Carlo simulation (e.g., the MISCAN simulation program⁵⁷).

Deterministic calculations have the advantage of being exact. However, if a model is complex, involving many possible events and intervening decisions based on those events, deterministic computations must exhaustively calculate the probability of every possible combination of events and decisions. In problems of even moderate complexity, this may involve millions of combinations. Stochastic models are, in essence, empirical samplings from these combinations, so that each combination appears in the final counts in proportion to its likelihood.

In addition to greater ease of complex simulation, stochastic models have the advantage of yielding not only average effects, but also measures of the uncertainty around the computed average (i.e., they can provide a confidence interval); deterministic calculations yield a point estimate only. A limitation of stochastic models is that complex simulations require intricate knowledge of the disease's natural history to estimate the parameters of the simulation. In the absence of such knowledge, the analyst must make the most reasonable assumptions about disease history. In either deterministic or stochastic modeling, lack of knowledge may be addressed through sensitivity analyses—varying the model parameters through reasonable ranges to observe the effect on the results. Generally it is desirable to use the simplest model possible, for which critical data are available for describing the parameters and their interrelationships.

Other Issues in Modeling to Estimate Effectiveness

Several issues germane to modeling will be briefly reviewed in this section, including specification of param-

ters and modeling patient characteristics, use of disease-specific or total mortality data, using models to "correct" for lead time and length biases, and model validation.

Specification of Survival Parameters and Modeling Patient Characteristics. Clinical trials and observational studies typically provide estimates of risk reduction or relative risk during the follow-up period, but give little indication how to estimate the survival curve for individuals beyond the end of the trial. Moreover, a trial restricted to a particular demographic or clinical group begs the question of what the effect might be in persons of younger or older ages, persons of the opposite sex, or persons with comorbidities. Thus, the analyst must make assumptions regarding the appropriate basis for extrapolation beyond the period of observation and to populations with different survival curves. For example, in a CEA comparing two thrombolytic therapies for acute myocardial infarction, the analysts used primary data from an RCT to estimate 1-year survival and then extended the observation period by modeling survival based on a separate database of patients with coronary heart disease.⁵⁵

The simplest assumption to make is that the age- and sex-specific risk of death for the affected population is modified by the disease in question, the intervention being evaluated, and any comorbidities that affect survival relative to the general population. A key choice is whether these three effects are additive or multiplicative.

Event probabilities in CEA models are often represented as conditional on patient characteristics, including age, gender, risk factors, stage of disease, and prior morbid events.⁵⁸⁻⁶² These probabilities can be estimated separately for relevant subpopulations when data permit, but more often they are specified by an equation derived assuming a statistical relation between event probabilities and patient characteristics. The predictive equations can be derived using logistic regression, Poisson regression, proportional hazards models, or Bayesian analysis, to name a few techniques. These analyses can assume independence among the characteristics, or they may allow for interactions (e.g., effect modification); they can also be additive or multiplicative. Proportional hazard models and the logistic regression models are both essentially multiplicative. The declining exponential approximation to life expectancy (DEALE) model uses an additive function of risk factors.^{63,64} The implications of the choice of an additive versus a multiplicative assumption can be striking.^{9,10,47,65-68} When practical, sensitivity analysis should be used to evaluate different assumptions about parameter form.

Disease-Specific and All-Cause Mortality. Estimating length of life is a central problem in CEA. The main end point in many trials is disease-specific mortality—that is, mortality due to the disease addressed by the trial. However, the disease-specific mortality may be only part of the picture. For example, in estimating the effectiveness of cholesterol-lowering drugs to reduce deaths from cardio-

vascular disease, use of cardiovascular disease-specific mortality will overstate effectiveness if the intervention also leads to a higher rate of death from other causes.^{69,70}

Another caveat regarding the use of disease-specific mortality to estimate effectiveness in a CEA concerns misclassification.^{71,72} In RCTs, in which the investigators have drawn careful protocols for attribution of cause of death and can make this determination in follow-up of study participants, the attributed disease-specific mortality rates may be useful inputs to the CEA modeling process. However, in less-controlled studies, there may be either an underreporting or overreporting of disease-specific causes. Thus, it is suggested that CEAs use all-cause mortality as the basis for estimating life expectancy gains.

Use of Modeling to Address Lead Time and Length Biases. Two related types of bias—lead time and length—make it difficult to determine with certainty if a screening intervention is effective in improving outcomes seen in nonrandomized controlled studies;^{15,73-75} modeling can be used to "correct" estimates of effectiveness for these biases. Lead time in a screening program is the time, in the normal course of disease, between the average time of early diagnosis by screening or case finding, and the average time of diagnosis in the absence of screening. Lead time bias is an overestimate of the increased survival associated with screening, owing to the fact that the disease is diagnosed earlier in its natural history. In extreme cases, all of the observed increase in survival with screening may be attributable to lead time bias, and there may be no actual prolongation of life.^{74,75} Lead time may have another consequence that is important for effectiveness estimation: earlier diagnosis and treatment afforded by screening may expose the patient to a longer period of adverse treatment effects than would occur in the absence of screening.

Length bias refers to the tendency for slower-growing, less-virulent disease to be detected in a screening program more often than more aggressive disease. As a result, those with aggressive disease are underrepresented in screened populations, and patients detected by screening may do better than unscreened patients, regardless of whether screening actually influences outcome, leading to an overestimation of effectiveness.^{15,74}

The analyst can address these biases by modeling the disease process directly; this requires estimates of such variables as tumor progression, stage-specific screening sensitivity, and stage-specific treatment response. One simulation model that incorporates such disease process modeling to avoid lead time and length biases is the MISCAN model.⁵⁷ For examples of this, and other approaches, the reader is referred to other sources.^{49,58-62,76-79}

Model Validation. Models often cannot be validated directly. The results of a model should, therefore, be accompanied by sensitivity analyses identifying which model inputs and parameters exert the most leverage on outputs. However, some aspects of models, such as which vari-

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Breast and Cervix Cancer Screening among Multiethnic Women: Role of Age, Health, and Source of Care¹

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Objective. The aim of this study was to evaluate the relationships between age, health status, access to care, and breast and cervical cancer screening among multiethnic elderly and nonelderly women.

Methods. A structured telephone survey of a quota sample of 1,420 New York City women from four Hispanic groups (Columbian, Dominican, Puerto Rican, Ecuadorian) and three black groups (U.S., Caribbean, and Haitian) was performed. Outcome measures included "ever" and "recent" self-reported use of mammography, clinical breast examination (CBE), and Pap smears. Logistic regression models assessed the predictors of screening use.

Results. Having a regular source of care significantly predicted all screening use for both elderly and nonelderly, controlling for ethnicity, sociodemographics, health status, access to care, proportion of life in the United States, and cancer attitudes. Elderly women (≥ 65 years) were significantly less likely to have ever had (OR = 0.79, 95% CI 0.65-0.96) and to have recently had (OR = 0.67, 95% CI 0.57-0.79) Pap smears than younger women, controlling for the other variables; being elderly also tended to be an independent predictor of ever and recent mammography and CBE use. Interestingly, there was a trend for health status to act differently in predicting Pap smear use for the two age groups. For younger women, being in poor health increased the odds of Pap smear screening, while for elderly women, being in good health increased the odds of screening.

Conclusions. Elderly women reported being

screened less than younger women; interactions between health status and age need further exploration. ©1999 American Health Foundation and Academic Press

Key Words: mass screening; breast cancer; cervical cancer, elderly; ethnicity.

INTRODUCTION

Women ages 65 and over represent 13% of the U.S. population, but constitute the majority of new cases of, and deaths from, breast cancer; this age group also represents a disproportionate 25% of new cases of and 43% of the deaths from cervical cancer. [1] The elderly subgroups most likely to develop and/or die of breast and cervical cancer include socioeconomically disadvantaged and minority women [2-7].

Effective early detection tests are available for breast and cervical cancer. Unfortunately, despite impressive overall gains in use of mammography and Pap smears [8], the elderly [8-11], especially minority elderly [8,9], remain underrepresented in screening programs. For all age, socioeconomic, and ethnic groups, one of the most powerful predictors of screening is having a physician recommendation [12]. However, physicians are less likely to recommend screening to their older, compared to their younger, patients [13,14]. There are little data on other determinants of screening in elderly women [15] and still less is known about minority elderly.

Using data from a study of the cancer control needs of three black and four Hispanic urban groups, we examined whether age mediated breast and cervical cancer screening use in this multiethnic target population. We hypothesized that, despite having a regular source of care, elderly women from all ethnic groups would be screened at lower rates than younger women and that poorer health status would be associated with lower screening use among elderly, but not younger, women.

¹ Supported by Grant RO1 CA49573 (J.K.) from the National Cancer Institute and in part by Grant RO1 AG15430 (J.S.M.) from the National Institute on Aging, Grant RO1 HS 08395 (J.S.M.) from the Agency for Health Care Policy and Research, and Grant DAMD 17-97-1-7131 from the Department of the Army (A.S.O.).

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METHODS

This paper reports on data from an IRB-approved, National Cancer Institute-funded project to describe the smoking, diet, alcohol use, and cancer screening practices of Caribbean, Haitian, and U.S. blacks and Puerto Rican, Dominican, Columbian, and Ecuadorian Hispanics living in New York City (NYC). These groups represented the major ethnic subgroups living in NYC at the time of the study [16]. A structured 20- to 30-minute telephone survey was conducted by trained, multilingual staff between May and November, 1992, to assess health behaviors, cancer knowledge, attitudes and beliefs, screening use, access to medical care, acculturation, and sociodemographics. This report focuses on the breast- and cervical-cancer-related data.

Study Population

A quota sampling method, stratified by four age categories (18–44, 45–54, 55–64, and 65–74 years), was used to identify 50 women from each ethnic group (except Haitians, $n = 25$ per age group). This method has been described elsewhere [17]. Briefly, to target households with listed and unlisted numbers, a dual sample design was utilized and included a full list frame sample selected from telephone directories and a sample selected by random digit dialing. The random digit dialing (RDD) sample used a two-stage RDD cluster design adapted from Waksberg [18]. First, to obtain the quotas and control screening and interviewing costs, criss-cross directories were used to identify the exchanges in areas where a high percentage of the target populations were known to reside; next, random samples were selected from these exchanges.

Calls were made to 19,300 telephone numbers: 2,514 identified eligible subjects (based on age and ethnicity), 10,478 had no eligibles, and eligibility status was unknown for 6,308 (due to refusal of screen, language barrier, or not contacted once quota was met). Thus, approximately eight calls were made to identify one eligible subject. All calls are considered in calculating the overall survey response rate. If more than one eligible person lived in the household, the individual with the most recent birthday was chosen.

To promote participation, advertisements about the study were placed on local radio stations, in newspapers and subways, and on community bulletin boards. These advertisements included the fact that participants would be entered in a lottery with prizes ranging from \$100 to \$1,000.

Interview

The interview was developed using existing national survey items and modified for use in the target populations. The interview content areas were reviewed by

focus group participants ($n = 95$, participating in 15 groups recruited from community groups and clinics and public hospitals) and community advisors. Participants and advisors were selected to represent all 7 ethnic groups. Spanish- and Haitian-language translations were developed using translation, back-translation, and resolution of cultural appropriateness through review by community advisors. Computer-assisted telephone interviews were conducted in the respondent's language of choice. An original call and up to seven call-backs were placed day and evening, 7 days a week, before a respondent was considered a non-participant.

Variables

The outcome variables were ever/never and recently/not recently having a mammogram, clinical breast examination (CBE), or Pap smear. Recent was defined for mammography as ≤ 2 years for women ages 40 to 49 years, and ≤ 1 year for women 50 years and older; for CBE as ≤ 1 year for women 18 years and over; and for Pap smear as ≤ 3 years for women 18 years and over, based on National Cancer Institute recommendations in 1992 [12]. Before questions on use were asked, each screening modality was described in detail. Independent variables included age, sociodemographics, health/health care factors, attitudes, and an acculturation indicator.

Age was measured in four groups (18–44, 45–54, 55–64, and 65+ years); these groups were also collapsed to two groups (< 65 and ≥ 65 years). An age-related screening "rigor" variable was also included, reflecting the fact that the quota ages included groups of women with differing periodicity of screening recommendations. Sociodemographic variables included race/ethnicity (seven groups or collapsed into two groups—black and Hispanic), education (< 12 vs ≥ 12 th grade), marital status (married/living as married vs not), and employment (working vs nonworking). Health status was evaluated using a five-level summary measure (Compared to other people your age, would you say your health is . . . ? [19]) based on relationships with screening, this variable was also categorized into two levels (good, very good, and excellent vs fair and poor). Access to care variables included source of care (no regular source, having a regular source, and having a regular physician at that source), settings of care (public and hospital out-patient clinics, HMOs, and private offices), and insurance (insured vs uninsured).

Cancer attitudes were measured using the Cancer Attitudes scale [20]. This scale includes an anxiety subscale (six items; Kuder–Richardson(KR) [21] = 0.58), a hopelessness subscale (eight items; KR = 0.72), and a denial subscale (two items; KR = 0.46); based on similar factor loadings, distributions, and relationships to

screening, these subscales were combined for this analysis into a single measure ($KR = 0.75$), where a higher score reflects having less anxiety and hopelessness and a lower level of denial. In addition, other cancer "superstitious" beliefs (e.g., not having faith in God, not being a good person, or having another person wish bad things about you . . . increase your chances of getting cancer) and embarrassment about being examined were included.

Acculturation was measured as the proportion of life spent in the mainland U.S. (<1 year, $\leq 25\%$, 26–50%, 51–75%, >75%, and U.S.-born); these data were also collapsed into two categories (high as $\geq 50\%$ and low as <50% or U.S.-born). Our data included several other potential measures of acculturation, including language of the interview, age of immigration to the United States, and a validated adaptation of a 26-item linguistic acculturation scale [17,22,23], although the latter two were only asked of non-U.S.-born and non-English speakers, respectively. Also, many women who immigrate late in life continue to use their native language, but may assimilate health behaviors over time [24]. For all of these reasons, we chose the proportion of life in the United States as a proxy for acculturation in these analyses. Regression results were comparable using alternative acculturation measures among Hispanics (data not shown).

Data Analysis

Categorical variables were collapsed into two or three levels, as described above; median values were used to create dichotomous groups for continuous variables. Bivariate relationships between independent variables and screening use were examined first; χ^2 tests were used to assess statistical significance. To explore interactions in screening use by age, data were examined stratified by age (<65 and ≥ 65). We were specifically interested in interactions between the following groups

of variables and screening use: age and health, age and source of care, and age and attitudes. Based on initial data analyses, we also examined interactions between education and attitudes, ethnicity and attitudes, and ethnicity and folk beliefs. If there appeared to be an interaction in stratified analyses, we next performed a logistic regression including the main effect and the interaction term. Since we examined many potential interactions, we only retained interaction terms for final analysis that were significant, controlling for the main effect. Finally, we developed a logistic regression model for each screening outcome. Blocks of variables were entered in the following order: age, sociodemographics, health status, access, attitudes, acculturation, and interactions. After the addition of each block, we examined whether added variables changed coefficients of variables already in the model (ie, confounded). Variables that were not significant in any model were deleted; variables which were important in some, but not all, models were retained for comparability. Model goodness of fit was assessed by the -2 log likelihood (the change from the intercept-only model to the full model) and the c values (where 1 indicates perfect prediction) [25].

RESULTS

Response Rate

The overall survey response rate was 62.3% (including calls made to identify homes with women of the age and ethnic group of interest) and was similar for younger and older women. Among respondents who qualified for the survey based on age and ethnicity, the refusal rate was only 2.1%. Among the 1,420 women in the final sample, 43.5% completed the survey in English, 51.3% in Spanish, and 5.2% in Creole.

TABLE 1
Unadjusted Screening Rates by Age

Age group	n	Mammogram		Clinical breast exam		Pap smear	
		Ever	Recent ^a	Ever	Recent ^a	Ever	Recent ^a
18–44 ^b	516	79.8%	70.8%	85.9%	68.8%	88.9%	72.0%
45–54	327	64.3	52.0	85.3	62.0	90.7	63.7
55–64	314	70.6	52.2	87.6	66.1	86.2	54.7
≥ 65	275	73.5	48.7	85.4	56.0	81.2	48.5
P value ^c	—	0.012	0.001	NS	0.002	0.004	0.001
Total	1414	70%	53.0%	86.0%	64.6%	87.3%	62%

Note. NS, not significant; n, sample size.

^a Recent is defined as the proportion of women having a recent screen among all women.

^b In this age group ever and recent mammography only applies to women ages 40–44 years ($n = 94$).

^c χ^2 .

Bivariate Determinants of Screening Use

Overall 70, 86, and 87.3% of women reported ever having a mammogram, CBE, and Pap smear, respectively, and 53, 64.6, and 62% reported having had these tests recently. Table 1 summarizes unadjusted screening rates by age. Generally, women 65 and over were the least likely to not to be recently screened, or in some cases to have ever been screened.

Table 2 presents the relationship between other participant characteristics and screening. Briefly, ethnicity, insurance, reporting a regular source of care, and attitudes were each significantly related to ever and recent use of all three tests, and Haitian women reported the lowest screening rates of all ethnic groups. Women who spent a greater proportion of their lives in

the United States were significantly more likely to have ever and recently had breast cancer screening than women living in the United States for less time. Interestingly, the effects of attitude varied across ethnic groups (data not shown). While negative attitudes (greater anxiety, hopelessness, and denial) were held more often by Hispanic women (range 59.9–65.5% for Hispanics; 38–39.5% for blacks), the relationship between screening and attitude was significant more often for black women. For instance, negative attitudes significantly decreased the rate of ever having mammography and Pap smears only for the black groups, but not for the Hispanic groups (data not shown).

Education was significantly related to all categories of test use except ever having had a mammogram.

TABLE 2
Unadjusted Screening Rates by Participant Characteristics Overall ($n = 1,420$)

Variable	Mammography		Clinical breast examination		Pap Smear	
	Ever ($n = 989$)	Recent	Ever ($n = 1414$)	Recent	Ever ($n = 1400$)	Recent
Age						
≥ 65 years	73.5%	48.7%	85.4%	56.0%	81.2%	66.7%
< 65 years	70.0 $P = 0.12$	53.1 $P = 0.28$	86.7 $P = 0.75$	72.6 $P = 0.001$	88.2 $P = 0.02$	80.8 $P = 0.001$
Ethnicity						
Columbian	74.8	53.0	87.6	69.2	79.2	71.8
Dominican	74.4	51.7	79.8	66.9	88.3	78.9
Ecuadorian	69.1	53.3	85.3	70.1	89.3	80.8
Puerto Rican	76.5	61.1	92.3	73.9	86.3	80.6
U.S.-born black	73.0	54.2	92.8	78.5	94.7	81.8
Haitian	43.5	33.8	79.4	69.7	74.0	68.9
Caribbean	68.2 $P = 0.001$	47.5 $P = 0.014$	83.4 $P = 0.001$	62.3 $P = 0.014$	92.4 $P = 0.001$	83.0 $P = 0.014$
Education						
≥ 12 th grade	72.5	56.5	89.3	77.5	90.0	82.7
< 12 th grade	67.5 $P = 0.09$	47.3 $P = 0.005$	81.1 $P = 0.001$	58.5 $P = 0.001$	83.0 $P = 0.001$	72.3 $P = 0.001$
Insurance						
Yes (public or private)	73.9	55.8	87.7	73.2	88.6	80.8
No (uninsured)	54.9 $P = 0.001$	37.8 $P = 0.001$	79.5 $P = 0.001$	57.6 $P = 0.001$	82.1 $P = 0.003$	70.1 $P = 0.001$
Regular source of care						
Yes (regular source) ^a	73.0	54.6	88.0	72.3	88.4	80.6
No (no regular source)	48.2 $P = 0.001$	33.6 $P = 0.001$	73.7 $P = 0.001$	55.3 $P = 0.001$	80.1 $P = 0.002$	66.3 $P = 0.001$
Site of care						
Public	78.0	59.3	87.3	73.5	89.5	82.0
HMO	80.3	59.0	90.4	73.9	91.6	80.8
Private	69.0 $P = 0.005$	51.1 $P = 0.067$	88.4 $P = 0.567$	71.2 $P = 0.648$	87.3 $P = 0.234$	80.1 $P = 0.75$
Health status						
Excellent, very good, good	70.2%	55.2%	88.3%	72.8%	88.0%	80.2%
Fair, poor	70.1 $P = 0.98$	50.2 $P = 0.17$	84.6 $P = 0.05$	68.2 $P = 0.07$	86.8 $P = 0.49$	77.6 $P = 0.25$
Proportion of life in the U.S. (acculturation)						
High ($\geq 50\%$ or U.S. born)	76.3	58.5	90.5	80.2	89.3	79.9
Low ($< 50\%$ of life in U.S.)	67.9 $P = 0.01$	49.9 $P = 0.019$	83.7 $P = 0.001$	64.7 $P = 0.001$	86.2 $P = 0.10$	78.0 $P = 0.40$
Cancer attitudes						
Negative	66.7	46.6	81.3	59.6	83.8	72.0
Positive	73.6 $P = 0.02$	57.7 $P = 0.001$	89.9 $P = 0.001$	78.1 $P = 0.001$	89.8 $P = 0.001$	83.7 $P = 0.001$
Other cancer beliefs						
Yes	69.8	47.6	83.5	60.2	84.7	73.9
No	70.4 $P = 0.85$	54.2 $P = 0.06$	87.0 $P = 0.094$	73.5 $P = 0.001$	88.2 $P = 0.08$	80.0 $P = 0.009$

^a Regular care includes having a regular place, with or without having a regular doctor at that place.

There was also an interaction between attitudes and education that predicted screening use. Women of higher education were more likely to be screened if they held more positive attitudes; for women with more negative attitudes, education did not predict screening use, indicating that attitudes may interact with education in predicting screening (data not shown).

In age-stratified analyses, the effect of health status was mediated by age for Pap smear screening: among younger women, those with poorer health were more likely than those in better health to have ever (91% vs 87%, $P = 0.05$) or recently had a Pap (85% vs 79%, $P = 0.01$). In contrast, among elderly women, those in poorer health were less likely to be screened than those in better health (74% vs 85%, $P = 0.03$, for ever and 58% vs 71%, $P = 0.04$, for recent Pap). Greater proportion of life in the United States significantly increased all screening use for younger, but not elderly, women (data not shown). Lastly, there was an age-cancer belief interaction, where younger women with lower "superstitious" beliefs were more likely than those with higher levels of these beliefs to ever have a CBE (87.3% vs 82.5, $P = 0.05$) and a recent mammogram (56.2% vs 47.6, $P = 0.04$), CBE (76.3% vs 62.3%, $P = 0.001$), and Pap smear (82.8% vs 77.5%, $P = 0.05$); among elderly women there was no relationship between such beliefs and screening. Relationships between age, care, and screening could not be assessed since, after stratifying by age, too few women had no source of care.

Logistic Regression Models of Screening Use

Breast cancer screening use. Overall, the strongest single independent predictor of breast cancer screening was having a usual source of care. Women with a usual source of care were over 200% more likely to have ever, or recently, had both screening modalities as women without a usual source of care, controlling for the remaining variables (Table 3). Other measures of access to care were also significant independent predictors of ever and recent mammography use.

The next most important predictor of breast cancer screening was attitude. Women with the most negative attitudes were between 40 and 60% less likely to have ever or recently been screened using either modality. As was seen in the stratified analyses, there was an interaction between ethnicity and attitude, with black women with negative attitudes less likely to be screened than Hispanic women with comparable attitudes.

There was no significant age effect for use of either breast cancer screening modality, although point estimates indicate that elderly women may have been screened less often than younger women. Health and interactions between health and age were also not significantly related to screening. Goodness of fit calculations indicated strong predictive power for all models:

$c = 0.70$, where 1 indicates perfect prediction (ever mammography and CBE) and $c = 0.69$ (recent mammography) and $c = 0.73$ (recent CBE).

Cervical cancer screening. Access to care variables were again the most important predictors of screening, followed by attitudes (Table 3). Elderly women were 21 and 33% less likely to have ever had or to have had a recent Pap smear than younger women, controlling for sociodemographics, health, access to care, time in the United States, and attitudes. As hypothesized, there was an interaction between age and health, with younger women in poor health more likely to have ever had or to recently have had a Pap smear, and elderly women in good health more likely to have been screened. Model goodness of fit was very good for both ever ($c = 0.70$) and recent Pap use ($c = 0.69$).

DISCUSSION

This is one of the first studies to describe the interrelationships between age, having a usual source of care, and health status on breast and cervical cancer screening use in multiethnic elderly and nonelderly women. For women of all ages, access to care variables, including having a usual source of care and being insured, were the strongest predictors of screening use. Our first hypothesis, that elderly women would report lower screening rates than younger women, controlling for having a usual source of care and other variables, was true for Pap smear screening; there was also a weak trend for lower breast cancer screening among elderly compared to nonelderly women. We also found an interesting effect of age and health on cervical cancer screening use. Younger women with poorer health were more likely to be screened, while elderly women with good health were most likely to be screened, compared to other groups.

Research on the impact of health status on cancer screening has been limited and inconsistent. In one study, we previously found that elderly women with a greater number of chronic illnesses were more likely to participate in breast and cervical cancer screening than those with fewer illnesses [26]. We hypothesized that women with more illnesses attended clinic more often and were exposed to greater opportunities to be screened. Alternatively, sicker women may have had a greater sense of susceptibility to illness, including cancer, that motivated them to be screened. Others have found chronic disease to both increase [27-29] and decrease [30-32] cancer screening use. Our finding of an interaction between health status and age suggests that physicians (and patients) are behaving differently in response to illness level according to the patients' age. For younger women, it is possible that poor health likely leads to greater interaction with the system and increased opportunity for screening; the physicians may

TABLE 3
Adjusted Odds^a of Breast and Cervical Cancer Screening

Variable	Mammography		Clinical breast examination		Pap smear	
	Ever <i>n</i> = 989 Odds ratio (95% CI)	Recent <i>n</i> = 945 Odds ratio (95% CI)	Ever <i>n</i> = 1414 Odds ratio (95% CI)	Recent <i>n</i> = 1388 Odds ratio (95% CI)	Ever <i>n</i> = 1400 Odds ratio (95% CI)	Recent <i>n</i> = 1420 Odds ratio (95% CI)
Age						
≥65 years	0.88 (0.65–1.19)	0.99 (0.75–1.31)	0.98 (0.73–1.30)	1.05 (0.86–1.29)	0.79 (0.65–0.96)	0.67 (0.57–0.79)
<65 years	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Education						
≥12th grade	1.18 (0.85–1.64)	1.20 (0.88–1.63)	1.60 (1.13–2.27)	1.59 (1.20–2.11)	1.33 (0.93–1.90)	1.24 (0.92–1.67)
<12th grade	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Insurance						
Yes (public or private)	1.99 (1.37–2.89)	1.96 (1.35–2.84)	1.25 (0.86–1.82)	1.81 (1.32–2.50)	1.36 (0.91–2.02)	1.55 (1.11–2.16)
No (uninsured)	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Regular source of care						
Yes (regular source) ^b	2.53 (1.63–3.93)	2.05 (1.30–3.24)	2.18 (1.46–3.24)	2.10 (1.45–3.02)	1.78 (1.15–2.76)	2.06 (1.43–2.97)
No	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Site of care						
Public	1.82 (1.29–2.56)	1.70 (1.24–2.33)	1.12 (0.79–1.58)	1.27 (0.95–1.68)	1.16 (0.81–1.67)	1.23 (0.91–1.66)
HMO	1.79 (1.14–2.80)	1.52 (1.02–2.27)	1.31 (0.79–2.18)	1.27 (0.87–1.85)	1.70 (0.97–2.97)	1.28 (0.85–1.94)
Private	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Health status						
Excellent, very good	0.87 (0.62–1.25)	0.74 (0.54–1.03)	0.78 (0.556–1.12)	1.07 (0.80–1.43)	0.98 (0.68–1.43)	0.90 (0.66–1.23)
Good, fair, poor	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Proportion of life in the U.S. (acculturation)						
High (≥50% or U.S. born)	1.35 (0.95–1.9)	1.40 (1.35–2.84)	1.01 (0.86–1.95)	1.66 (1.56–2.37)	1.18 (0.81–1.73)	1.35 (0.99–1.84)
Low (<50% of life in the U.S.)	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Cancer attitudes						
Negative	0.48 (0.29–0.77)	0.40 (0.24–0.63)	0.69 (0.40–1.19)	0.59 (0.39–0.91)	0.38 (0.20–0.72)	0.45 (0.28–0.71)
Positive	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Other cancer beliefs						
Yes	1.58 (0.87–2.84)	1.61 (0.91–2.86)	1.11 (0.56–2.21)	1.03 (0.60–1.76)	1.01 (0.48–2.12)	1.13 (0.63–2.03)
No	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —	1.00 —
Interaction terms						
Health* age	NS	NS	NS	NS	**	**
Acculturation* age	NS	*	*	NS	NS	NS
Ethnicity* attitude	**	*	*	NS	*	*
Ethnicity* folk beliefs	**	*	NS	NS	NS	NS

Note. CI, confidence interval; NS, not significant.

^a The effects of each variable adjusted for ethnicity and the remaining variables in logistic regression analysis.

^b Regular care includes having a regular place, with or without having a regular doctor at that place.

^c The seven ethnic groups are collapsed into two groups—Hispanic and black—for testing interaction terms.

* $P < 0.05$.

** $0.10 < P < 0.06$.

feel these women should be screened regardless of health condition. For elderly women, there may be some triage going on, with a decision to screen those in good health more often than those in poorer health. Given that physicians consistently underestimate elderly women's life expectancy [13], this triaging may or may not be appropriate [33–35]. For instance, breast cancer screening has been noted to save years of life for elderly women with comorbid conditions [36]. Given the increase in both cancer risk and comorbidity with advancing age, these are important areas for future research.

Our finding that access to care increases screening

use for multiethnic women is consistent with previous research in nonelderly [37] and elderly populations [13]. Unfortunately, we could not separate the effects of having a regular source of care and having a physician recommendation for screening, since we did not measure perceptions of screening advice.

While not a primary focus of our research, we noted interesting interactions between ethnicity and attitudes toward cancer and attitudes and educational level. Further research will be important to delineate the pathways whereby these variables act to produce observed behaviors; understanding these relationships

can be an important guide to the development of interventions targeted to specific subgroups of these high-risk multiethnic populations.

There are several caveats that should be considered in evaluating our results, including use of self-report, external validity, response rate, and secular trends in screening. Use of screening was determined by self-report. Since women received care from a very large number of diverse settings, it was not practical to validate self-reports through medical record reviews. Also, we judged that requests for written record release would decrease overall survey response rate. Most studies of self-reported Pap smear and mammography use find self-report to be fairly accurate for crude time periods, even among older and socioeconomically diverse groups [38], although women may overestimate their use of screening [38-43]. Since we have no reason to expect that the validity of self-report varied systematically across age and health groups, any overestimation of screening use should have decreased our ability to find significant differences.

We used a pragmatic approach to enroll sufficient numbers of multiethnic women using adaptations of population-based random-digit dialing telephone survey methods. This, coupled with the focus on households with telephones in one urban city, may limit the external validity of the results. However, the results for our sample are similar to those from national samples of women (Kerner and Breen, unpublished data). Moreover, the use of area-probability sampling would not have yielded a sufficient number of elderly multiethnic women for analysis. While it is estimated that the proportion of black and Hispanics in NYC owning telephones is 78 to 85% (compared to 90% overall) [44], alternatives to telephone interviews (e.g., home interviews) are difficult to achieve in the economically depressed areas of NYC where the majority of the target population resided.

Our overall response rate of 62% is considered good for a survey of this type [45]; among respondents who qualified for the survey based on age and ethnicity, only 2.1% refused to complete the interview. Since we have no data on nonparticipants, we do not know if women included in the sample differed systematically from those not participating. Our sample had high education levels, suggesting some self-selection among participants. However, our screening rates were very similar to national rates among underserved black and Hispanic women in the same time period as our survey [46-49]. The high rates observed in the early to mid-1990s, compared to historically lower rates [11], may reflect successes of targeted public health programs [47]; alternatively women completing surveys may be more likely to participate in screening than nonsurvey participants [47]. Since there have been secular increases in screening use since this study was conducted,

it will be important to see if age- and health-related trends in use continue to be noted over time.

Overall, our results suggest that among urban, multiethnic women there are clinically important interactions between age, health, and use of screening. Further research is needed to delineate these relationships more precisely and to define the appropriate uses of cancer screening services among subpopulations of elderly women historically at risk for poor cancer outcomes.

ACKNOWLEDGMENTS

Portions of this work were conducted while Drs. Mandelblatt and Kerner and Ms. Cagney were at Memorial Sloan-Kettering Cancer Center, Department of Epidemiology and Biostatistics, New York, New York. The authors thank the women who participated in this project for their contributions and Ms. Kathy Summers for manuscript preparation. A special thanks is offered to the community organizations who advised us and helped to promote survey participation. These organizations include Bedford Stuyvesant Healthy Heart Program, Cancer Control Center of Harlem, Caribbean Women's Health Association, Healthwatch, Local 1199 in Manhattan, New York Task Force on Immigrant Health, SHARE-NY, St. Nicholas Neighborhood Preservation Corps in Queens, and Washington Heights-Inwood Healthy Heart Program. This article is dedicated to the memory of our friend, colleague, and project advisor, Rachel G. Fruchter, Ph.D., MPH, a tireless advocate for women's health care.

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Effectiveness of Interventions Designed to Increase Mammography Use: A Meta-Analysis of Provider-targeted Strategies¹

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Abstract

The objective of this study was to determine the effectiveness of interventions targeted at providers to enhance the use of mammography. We performed a meta-analysis and included United States studies that used a randomized or nonrandomized concurrent control design, had defined outcomes, and presented data that could be abstracted for reanalysis. Interventions were classified as behavioral, cognitive, or sociological and further categorized by the type of control group (active versus usual care). Data were combined using DerSimonian and Laird random effects models to yield summary effect sizes. Thirty-five studies met the inclusion criteria. All types of interventions targeted at providers were effective in increasing mammography rates. Behavioral interventions increased screening by 13.2% [95% confidence interval (CI), 7.8-18.4] as compared with usual care and by 6.8% (95% CI, 4.8-8.7) as compared with active controls. Cognitive intervention strategies improved mammography rates by 18.6% (95% CI, 12.8-24.4). Sociological interventions also had a similar magnitude of effect on screening rates (13.1% increase; 95% CI, 6.8-19.3). Interventions targeting both patients and providers were not significantly better at increasing screening than those targeting providers alone, and multiple approaches (e.g., behavioral and cognitive) were generally not more effective than a single approach. All interventions targeted at physicians were effective in increasing screening rates. Decisions to use a particular approach will depend on resources, expertise, feasibility, and cost effectiveness.

Introduction

Despite evidence that regular mammography screening can reduce breast cancer mortality (1-4), many women fail to receive mammography or adhere to recommended guidelines for routine ongoing screening. A proportion of this underuse is due to an apparent paradox: whereas physician recommendation is one of the strongest predictors of mammography use (5-6), the most frequent reason cited by women for failure to have mammography is that a physician did not recommend one (5-6).

To overcome this apparent paradox, numerous interventions have been developed to enhance physician ordering or recommendation of screening mammography. However, because of the large number of different interventions, numerous mechanisms of intervention action, and variability in study design, it is difficult to develop a cohesive recommendation to improving physician screening behaviors, particularly in high-risk patient populations. An earlier meta-analysis of physician-targeted interventions to improve the use of mammography screening and clinical breast examinations indicated that most interventions were effective in increasing screening, but the magnitude of this effect varied by the type of intervention (7). Since preparation of that report, more than 50 additional studies to increase mammography utilization have been published (8-58).

In this study, we performed an updated critical review of well-designed provider-targeted interventions designed to increase the use of mammography. We estimate overall effect sizes for specific types of interventions to determine the most effective strategies to increase mammography utilization.

Materials and Methods

Study Selection. We used the OVID search mechanism with MEDLINE for the years 1980-1998 to identify published English language articles on interventions to increase mammography utilization. The search strategy was as follows: we used the terms "mammography" or "breast neoplasms/prevention and control" to identify the subset of studies focused on mammography screening. We then developed a series of terms to identify settings in which interventions could take place (e.g., "primary health care," "gynecology," and "family physicians") and the terms "health education," "health behavior," "patient compliance," "patient acceptance of health care," "attitude to health," or "health promotion." The combination of these searches yielded 600 studies. Study abstracts were reviewed for evidence of prospective follow-up with either randomized assignment to an intervention or control group or a nonrandomly selected concurrent control group. Because interventions were designed to increase the recommendation of mammography, we include studies that used either outcomes of ordering screening or completion rates of screening. Studies that relied on physician estimates of mammography recommendations were excluded (28, 59) because such self-reports are often inaccurate. Pre/post

Received 2/25/99; revised 5/27/99; accepted 6/3/99.

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¹ Supported in part by the Agency for Health Care Policy and Research Grant HS 08395 (to J. S. M.), Grant DAMD17-94-J-4212 from the Department of the Army, a Breast Cancer Center grant (to J. S. M.), Grant RO1 CA72908 from the National Cancer Institute (to J. S. M. and K. R. Y.), and Grant 2T32CA09314 from the National Cancer Institute (to K. R. Y.). An earlier version of this work was part of a 1999 report prepared for the Institute of Medicine entitled *Access to Quality Cancer Care: Evaluating and Ensuring Equitable Services, Quality of Life, and Survival*.

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designs without controls and uncontrolled trials were excluded. Published abstracts were also excluded because they were judged to have too brief a description of methods for assessment.

Twenty-one studies met the inclusion criteria. Reference lists of the selected studies were also searched to identify other eligible studies, and a hand search of *Journal of General Internal Medicine*, *Medical Care*, *Preventive Medicine*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, and *Cancer Epidemiology, Biomarkers and Prevention* was conducted for June-August 1998. Fourteen additional studies were thus identified, yielding a total of 35 studies.

Data Abstraction. We classified interventions as cognitive, behavioral, or sociological (60). Cognitive strategies provide new information and education, increase existing knowledge, and clarify misperceptions. Interventions that provided education or audit of practice with feedback were classified as cognitive. Behavioral interventions alter cues or stimuli associated with screening behavior and included reminders or administrative office systems. Sociological interventions use social norms or peers to increase screening adherence. We classified interventions that altered the structure of care delivery, in many cases through the use of nurse practitioners, as sociological. We also classified interventions with multiple types of strategies (e.g., reminders, education) as behavioral and cognitive. Where a sufficient number of interventions were available, interventions were further classified by the type of control group used, active control and usual care control. Active control groups included a lower level of an intervention, such as routine reminders or flow sheets in patient charts. We defined usual care controls as situations in which no intervention associated with mammography utilization was performed. In settings where usual care included routine reminders or flow sheets in patient charts, these interventions were classified as having an active control group.

Interventions were also classified by the individuals or group they targeted: providers; providers and patients; or, in cases where individual providers or patients were not explicitly identified, communities. The interventions we classified as targeted to communities attempted to educate or remind large groups of individuals through the media, generalized educational efforts, newsletters, flyers, and posters rather than personalized contact.

Data were abstracted from studies using a standardized abstraction format to describe the type of intervention, characteristics of mammography outcome determination (patient self-report, medical charts, electronic records, or medical claims), the patient population, and intervention effectiveness. Studies with multiple interventions had these data abstracted where possible. Additionally, for studies with multiple assessment points over time, the first assessment was used in the combined analysis.

Data Analysis. The effect size and 95% CI³ were calculated for each intervention included in the study. For randomized studies, intervention effectiveness was calculated as the difference in mammography utilization between the intervention and control group at the end of the study. For nonrandomized concurrently controlled trials, the effect size was calculated as the difference between the rates postintervention and preintervention for the intervention group and the control group. The formulas we used to calculate variance for randomized and

nonrandomized concurrently controlled trials are listed in the Appendix.

Tests of homogeneity, the DerSimonian and Laird Q-statistic (61), were performed for interventions grouped by mechanism of action (behavioral, cognitive, or sociological) and the type of control group. This statistic, which compares the summary effect measure and within-study effect, was compared against a χ^2 distribution with a null hypothesis of homogeneity. Meta-Analyst software (62) was used to calculate DerSimonian and Laird random effects summary statistics and 95% CIs (61). These are reported separately for different types of interventions. All analyses were performed under the null hypothesis of no difference in mammography use between intervention and control.

To test the influence of a single intervention on summarized results, we performed sensitivity analysis by sequentially dropping each intervention and recalculating the summary statistics.

Results

Among the 35 studies in the final study sample, some included multiple interventions, and several targeted patients and providers. Overall, there were 23 behavioral interventions, 8 cognitive interventions, 5 sociological interventions, and 13 interventions that combined behavioral and cognitive approaches (Table 1; Refs. 10, 39–42, 49–53, and 63–73). Most were randomized controlled trials in university settings ($n = 23$). The majority of study populations were composed of white women and women ages 50 years and over. In the studies that reported mammography history, the most frequent rates of ever having had mammography were between 25% and 49%.

Behavioral Interventions. Provider-targeted behavioral interventions included a reminder or office system prompts. Nine used usual care comparison groups, and eight had active comparison groups (two that targeted providers and patients used usual care controls, and four had active controls) (Table 2; Refs. 10, 16, 39–44, and 63–72). Overall, the provider-targeted interventions with usual care controls had an effect of increasing mammography by 13.2% (95% CI, 7.8–18.4). The interventions using active controls were homogeneous, and the overall rate of mammography was 6.8% higher for women whose providers received behavioral interventions, as compared with active controls (95% CI, 4.8–8.7). Sensitivity analyses did not affect these estimates.

Behavioral interventions targeted at both providers and their patients were of comparable effectiveness as those targeting providers alone and showed a 20.5% increase (95% CI, 9.7–31.3) compared to usual care and an 8.9% increase (95% CI, 3.1–14.6) compared to active controls, although these estimates are based on a small number of studies.

Cognitive Interventions. Interventions based on theories of cognitive change typically identify provider attitudes toward screening and breast cancer and provide focused educational material directed at increasing compliance with ordering mammography. The interventions included in this sample used audit with feedback and educational sessions or materials (Table 3; Refs. 47, 48, 64, 66, 72, 74, and 75). Compared to usual care, cognitive interventions increase mammography by 18.6% (95% CI, 12.8–24.4).

A single cognitive intervention was targeted at both providers and patients. This intervention increased mammography use by 16% (95% CI, 7.3–24.7). Finally, three interventions targeted patients and providers in communities using cognitive strategies and increased screening by 9.6% (95% CI, 3.4–15.8).

³ The abbreviation used is: CI, confidence interval.

Table 1 Characteristics of intervention studies included in meta-analysis (*n* = 35)

	No.	Percentage (%)	Reference no.
Type of intervention ^a			
Targeting providers alone			
Behavioral			
Usual care control	9	18.4	39, 40, 63-68, 72
Active control	8	16.3	10, 41, 43, 44, 69-71
Cognitive			
Usual care control	4	8.2	64, 66, 72, 74
Cognitive and behavioral			
Usual care control	4	8.2	64, 72, 77, 78
Sociological			
Usual care control	2	4.1	49, 50
Active control	3	6.1	51-53
Targeting providers and patients			
Cognitive			
Usual care control	1	2.0	66
Cognitive and behavioral			
Usual care control	4	8.2	45, 54, 66, 74
Active control	2	4.1	46, 52
Behavioral			
Usual care control	2	4.1	40, 67
Active control	4	8.2	10, 16, 42, 69
Targeting communities			
Cognitive			
Usual care	3	6.1	47, 48, 75
Behavioral and cognitive			
Usual care control	3	6.1	55, 56, 58
Study design ^b			
Randomized control trial	23	65.7	10, 39-41, 63-67, 69-71, 77 16, 42, 43, 47, 50, 52-54, 68, 72
Concurrently controlled trial	12	34.3	44-46, 48, 49, 51, 55, 56, 58, 74, 75, 78
Outcome measure ^{b,c}			
Completed mammogram from radiology reports	3	8.6	40, 54, 77
Chart review/patient record	21	60.0	10, 39, 64-69, 72 16, 41-44, 51, 54, 74
Patient self-report	7	20.0	45-48, 56, 58, 75
Ordered/response to reminder	6	17.1	52, 55, 63, 70, 71, 78
Setting ^b			
University	10	28.6	40, 41, 63-67, 69-71, 74, 77, 78
Community	25	71.4	10, 42-44, 49, 50, 52, 53, 68, 72 16, 45-48, 54-56, 58, 75
Patient age (yrs) ^{b,c}			
40-49	16	45.7	10, 42, 43, 48, 49, 65-70, 72, 78 47, 54, 56
50-59	31	88.6	10, 40-42, 63, 65-71, 77 16, 43-46, 49, 50, 53, 72, 74, 75, 78 47, 48, 55, 56, 58, 73
60+	28	80.0	10, 39, 40, 42, 43, 63, 65-70 16, 44-49, 51, 52, 72, 74, 75 55, 56, 58
Not stated	1	2.9	64
Race ^{b,c}			
>30% white	13	37.1	40, 45-48, 50, 52, 67, 74, 75, 78 68
>30% black	11	31.4	10, 41, 43, 49, 51, 52, 63, 67, 69, 70, 74
>30% Asian	4	11.4	63, 65, 66, 78
Not stated	12	34.3	16, 39, 42, 44, 53-56, 58, 64, 72, 77
Proportion with prior mammograms ^{b,d}			
0-24%	4	11.4	42, 51, 69, 75
25-49%	13	37.1	10, 42, 44, 46, 50, 52, 54, 56, 66, 68, 70, 75 78
50-74%	7	20	10, 43, 45, 48, 49, 58, 78
Not stated	15	42.9	16, 39-41, 53, 63-65, 67, 71, 72, 74, 77 47, 55

^a Denominator is the number of interventions.^b Denominator is the number of studies.^c Categories may total more than 100% because some studies had multiple interventions or populations.^d Adherent at baseline or within the past 2 years.

Table 2 Behavioral interventions

	Reference no.	Sample size		Women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
Provider-targeted behavioral interventions with usual care control	63	NE ^a	NE	8%	2%	6	NE
	64	385	385	85 (22%)	23 (6%)	16	(11.2–20.8)
	65 ^b	116	116	37 (32%)	14 (12%)	20	(10.0–30.0)
	66 ^c	432	432	264 (61%) ^c	194 (45%) ^c	16	(9.4–22.6)
	67 ^b	76	85	23 (30%)	9 (11%)	20	(7.5–31.9)
	68 ^b	710	710	285 (40%) ^c	248 (35%) ^c	5	(–0.03–10.03)
	39 ^b	32	23	5 (16%)	1 (4%)	11.3	(–3.7–26.3)
	40 ^b	14	43	1 (7%)	2 (5%)	2	(–11.8–16.8)
	72 ^b	NE	NE	77%	57%	20	NE
Summary	Q-statistic 16.5					13.2	(7.8–18.4)
Provider-targeted interventions with active controls	70 ^b	639	623	173 (27%)	131 (21%)	6	(1.3–10.7)
	69 ^b	345	266	108 (31%)	73 (27%)	4	(–3.4–11.0)
	41 ^b	2,654	2,654	1433 (54%)	1247 (47%)	7	(4.3–9.7)
	71 ^b	341	313	112 (33%)	95 (30%)	2.4	(–4.7–9.5)
	10 ^b	370	381	118 (32%)	97 (25%)	6.6	(0.1–13.1)
	43 ^b	600	625	266 (44.3%)	222 (35.5%)	8.8	(3.3–14.3)
	44 ^d	3372	4308	Pre, 597 (17.7%) Post, 1612 (47.9%)	Pre, 482 (11.2%) Post, 1490 (34.6%)	6.8	(4.1–9.5)
	44	3746	4308	Pre, 472 (13%) Post, 1528 (41%)	Pre, 482 (11%) Post, 1490 (35%)	4.8	(2.2–7.3)
Summary	Q-statistic 17.4					6.8	(4.8–8.7)
Provider and patient interventions with usual care controls	67 ^b	61	85	19 (31%)	9 (11%)	21	(7.2–33.8)
	40	24	43	6 (25%)	2 (5%)	20	(1.5–38.5)
Summary	Q-statistic 0.0					20.5	(9.7–31.3)
Provider and patient interventions with active controls	69 ^b	332	266	90 (27%)	73 (27%)	–0.3	(–7.5–6.9)
	42 ^b	1382	1343	732 (53%)	551 (41%)	12	(9.4–14.6)
	10 ^b	388	381	122 (32%)	97 (25%)	6.1	(–0.3–12.5)
	16 ^b	1171	1171	362 (31%)	187 (16%)	14.9	(11.5–18.3)
Summary	Q-statistic 17.3					8.9	(3.1–14.6)

^a NE, not evaluable.^b Random control group.^c Performance score. Pre, preintervention; Post, postintervention.^d Nonrandomized concurrent control group.

Sociological Interventions. We identified five sociological interventions designed to increase mammography screening (Table 4; Refs. 49–53 and 76). These provider-targeted sociological interventions used nurse-based interventions or reorganization of the clinic. These interventions were heterogeneous; most of the heterogeneity was associated with a single intervention (50). Omitting that study, sociologic interventions improved mammography utilization by 13.1% (95% CI, 6.8–19.3). Including the one study that was heterogeneous ($Q = 34.0$) decreased the effect size only slightly to 11.1%, with a wider CI (95% CI, 0.2–22.1).

Interventions with Combined Modalities. In interventions that combined cognitive and behavioral strategies to reach providers, the combined effect was a 21.0% increase in mammography utilization (95% CI, 8.8–33.6) in contrast to usual care (Table 5; Refs. 45, 46, 52, 54–56, 58, 64, 66, 74, 77, and 78). When behavioral and cognitive strategies targeted at both providers and patients were combined, these studies were heterogeneous ($Q = 24.2$). Eliminating the study associated with heterogeneity (54) led to a combined increase in mammography utilization of 16.1% (95% CI, 11.6–20.7). Finally, when cog-

nitive and behavioral strategies are targeted to patients and providers in communities, interventions are no longer effective (1.1% increase; 95% CI, –6.8–9.0).

Discussion

Interventions designed to enhance provider ordering or recommendations for mammography are all generally effective in increasing screening rates, regardless of approach. Behavioral interventions increased screening by 13.2% (95% CI, 7.8–18.4) compared with usual care and by 6.8% (95% CI, 4.8–8.7) compared with active controls. Cognitive intervention strategies improved mammography rates by 18.6% (95% CI, 12.8–24.4), and sociological interventions also had an effect of similar magnitude on screening rates (13.1% increase, 95% CI, 6.8–19.3). In all cases, interventions were more effective in increasing mammography use when compared with usual care than with active controls. Interestingly, strategies that targeted both patients and providers were not significantly more effective than those targeting providers alone. Thus, decisions on the ultimate selection of an intervention to improve mammography

Table 3 Cognitive interventions

	Reference no.	Sample size		Women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
Provider-targeted cognitive interventions usual care controls	66 ^a	432	432	285 (66%) ^b	194 (45%) ^b	21	(14.7–27.6)
	64 ^a	385	385	77 (20%)	23 (6%)	14	(9.4–18.6)
	74 ^c	Post, 152 ^d	Post, 227	Pre, 34 (22%) Post, 94 (62%)	Pre, 45 (20%) Post, 81 (36%)	23.7	(10.6–36.6)
	72 ^a	NE	NE	71% 57%		14	NE
Summary	Q-statistic 4.3					18.6	(12.8–24.4)
Provider and patient-targeted interventions usual care controls	66	216	216	164 (76%) ^b	130 (60%) ^b	16	(7.3–24.7)
Community-targeted interventions active controls	75	Pre, 487 Post, 486	Pre, 484 Post, 484	Pre, 268 (55%) Post, 365 (75%)	Pre, 266 (55%) Post, 295 (61%)	14	(5.5–22.5)
	48 ^c	Pre, 331 Post, 461	Pre, 333 Post, 420	Pre, 163 (49%) Post, 241 (52%)	Pre, 183 (55%) Post, 241 (57%)	0.7	(–9.3–11.4)
	47 ^a	270	270	221 (82%)	194 (72%)	10.0	(3.0–17.0)
Summary	Q-statistic 7.8					9.6	(3.4–15.8)

^a Random control group.^b Performance score.^c Nonrandomized concurrent control group.^d Post, postintervention; Pre, preintervention; NE, not evaluable.

Table 4 Sociological interventions

	Reference no.	Sample size		Percentage of women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
Provider-targeted sociological interventions usual care controls	49 ^a	Pre, 327 ^b Post, 253	Pre, 739 Post, 739	Pre, 222 (68%) Post, 195 (77%)	Pre, 488 (66%) Post, 484 (67%) and 64% (65.5%)	9.5	(0.8–18.2)
	50 ^a	1536	1338	502 (32.7%)	455 (34.0%)	–1.3	(–4.8–2.2)
Active controls	51 ^a	Pre, 199 Post, 160	Pre, 155 Post, 159	Pre, 18.3% (36) Post, 40.0 (64)	Pre, 18.1% (28) Post, 18.2% (29)	21.6	(9.0–34.2)
	52 ^c	267	268	30.9% (83)	19.4% (52)	11.5	(4.2–18.8)
	53	NE	NE	31.2%	22.8%	8.4	NE
Summary	Q-statistic 3.0					13.1	(6.8–19.3)

^a Nonrandomized concurrent control group.^b Pre, preintervention; Post, postintervention; NE, not evaluable.^c Random control group.

receipt that targets providers should depend on feasibility, resources, expertise, and cost effectiveness.

Recent national estimates indicate that 56% of asymptomatic women over the age of 50 years have received a screening mammogram within the past 2 years (79). Although this figure is higher than in the previous decade (80), potentially as a result of increased attention from managed care and other organizations to practice profiles and physician report cards (81), many women are still not screened. With the use of provider-directed interventions, such as educational systems (82), an additional 2.25 to 6 million women would be screened, with a resultant down-staging of disease and an improvement in morbidity and mortality.

Our result of an average of a 6–21% increase in screening with provider interventions is similar to that found in our prior meta-analysis. In the earlier study, which separated interventions into similar categories, we noted that mammography rates could be increased by 6–14% (7). The magnitude of effect seen with provider-targeted interventions is similar to that seen for patient-specific interventions (83).

Contrary to intuition, the combination of provider- and patient-targeted strategies was not significantly more effective than provider-targeted interventions alone. This is also the case for interventions using multiple approaches (behavioral and cognitive) rather than single approaches. Possible explanations for the lack of synergy between these two effective individual approaches include lack of foundation in theories of patient-provider communication and/or theoretical models of behavior, inability to ensure full penetrance into both target populations, lack of ability to ensure fidelity of complex interventions, or true negative synergy through increased patient anxiety or misperceptions. This will be an important area for investigation in future factorially designed controlled trials.

There are some methodological limitations with the meta-analysis reported here, including heterogeneity among studies that were combined, differences in patient populations, inconsistencies in the unit of analysis used to calculate intervention effectiveness, multiple interventions from the same study, the combination of multiple measures of mammography utilization, inability to evaluate the actual penetrance of intervention to

Table 5 Cognitive and behavioral interventions

	Reference no.	Sample size		Women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
Provider-targeted interventions usual care control	77 ^a	290	138	93 (32%)	6 (4%)	28	(21.7-34.3)
	64 ^a	385	385	81 (21%)	23 (6%)	15	(10.4-19.8)
	78 ^b	NE ^c	NE	10.8%	1.7%	9.1	NE
	72 ^a	NE	NE	78%	57%	21	NE
Summary	Q = 9.8					21	(8.8-33.6)
Provider and patient-targeted interventions usual care controls	74 ^b	129	227	Pre, 31 (24%) Post, 70 (54%)	Pre, 45 (20%) Post, 81 (36%)	13.4	(1.7-25.1)
	66 ^a	216	216	162 (75%) ^d	108 (50%) ^d	25	(16.2-33.8)
	46 ^a	Pre, 451 Post, 445	Pre, 449 Post, 440	Pre, 185 (41%) Post, 276 (62%)	Pre, 175 (39%) Post, 189 (43%)	17.0	(7.9-26.1)
	54 ^{a,e}	227	194	56 (24.6%)	56 (28.7%)	-4.1	(-12.6-4.4)
Active control	52 ^a	267	268	76 (28.4%)	52 (19.4%)	9.0	(1.8-16.2)
	45	Pre, 465 Post, 475	Pre, 474 Post, 443	Pre, 184 (40%) Post, 333 (70%)	Pre, 174 (39%) Post, 258 (58%)	11	(2.2-20.0)
Summary	Q = 9.1					16.1	(11.6-20.7)
Community-targeted interventions usual care controls	55 ^b	NE	NE	Pre, 46.2% Post, 91.1%	Pre, 62.5% Post, 83.6%	23.8	NE
	56 ^b	Pre, 437 Post, 327	Pre, 401 Post, 314	Pre, 133 (30%) Post, 175 (54%)	Pre, 125 (31%) Post, 147 (47%)	7.8	(-2.1-17.7)
	58 ^b	Pre, 706 Post, 958	Pre, 555 Post, 739	Pre, 393 (56%) Post, 687 (72%)	Pre, 310 (56%) Post, 550 (74%)	-2.7	(-9.7-4.3)
Summary	Q = 7.7					1.1	(-6.8-9.0)

^a Random control group.^b Nonrandomized concurrent control group.^c NE, not evaluable; Pre, preintervention; Post, postintervention.^d Performance score.^e Excluded from quantitative analysis.

target population (e.g., did individuals in the target population actually receive the intervention), potential patient and provider selection biases, publication bias, and lack of data on intervention durability. We combined data from studies conducted in dissimilar populations or environments in which mammography screening is obtained. We attempted to make the groups of interventions as homogeneous as possible. However, because of a limited number of interventions in some categories, we had limited power to assess homogeneity. To test the effects of any heterogeneity, we used sensitivity analysis to sequentially remove each study and recalculate summary estimates to determine the independent impact of a single study on overall results. Several studies yielded inconsistent results when combined with others as a result of differences in setting (i.e., community providers versus university hospitals or clinics; Ref. 68), unit of analysis (50), outcome definition (71), or limited power (40).

All of the interventions reviewed here included control groups of similar women and were grouped according to the mechanism of intervention action. However, there are important differences in the women enrolled in the different types of interventions, which may affect the interpretation and comparison of these results. For example, most studies include white women, although some included minority women. Additionally, several of the studies included populations of women with high rates of previous mammography (10, 13, 84). Thus, comparisons among interventions and adaptation of interventions to dissimilar populations should be approached cautiously.

The majority of studies we identified randomized individual providers to receive either the intervention or control condition. However, some studies randomized providers by prac-

tice group (50, 52), yet these data are combined as if randomization occurred individually, and all observations are independent. Women treated by the same provider may be more similar in terms of mammography utilization than those recruited from a random sample or those that received a standardized intervention. If analyses were to incorporate the actual unit of randomization (e.g., practice group) or correlation among individuals, CIs would be wider, but the estimate of intervention effectiveness should remain unchanged.

In several cases, multiple interventions were performed and reported within a single study (52, 64, 66, 67, 69, 72), but they were compared to the same control group. In one group of interventions, behavioral interventions with active control groups, two interventions from the same study are included in the quantitative analysis (44). Because individuals in the control group are counted more than once, assumptions of independence among subjects are violated. To assess the impact on the summary estimates and their interpretation, we recalculated these statistics twice, without one of the interventions each time. Excluding either one of the interventions did not affect the interpretation of summary statistics. In no other case was more than one intervention from a single study included in the calculation of summary statistics.

The studies included here used several mechanisms to identify mammography utilization: (a) patient self-report; (b) chart audit; (c) electronic claims; (d) mammography facility records of actual screening; and (e) documentation of provider ordering of a mammogram. We considered these different sources to be equivalent for the purposes of analysis, although this is not necessarily the case. Patient self-report of mammography has been described as highly correlated with mammography use reported in patient charts or claims, but it is likely to

overstate utilization (59, 85–87), particularly among low-income minority populations (88). However, women randomized to intervention and control provider groups might be equally likely to overstate mammography utilization, so whereas the absolute estimate of mammography utilization might be influenced by the reporting source, the relative estimate (intervention *versus* control) is less likely to be affected. In studies that reported provider ordering and actual patient completion of screening, interventions were more effective in increasing rates of ordering than rates of completion (50, 74). Again, this may overestimate the magnitude of effectiveness of interventions, but not the relative efficacy of each strategy.

The effectiveness reported here may not reflect the potential efficacy if the intervention had 100% penetrance. However, we cannot evaluate the degree of penetrance or the minimum level required to increase rates of screening. Women and providers participating in the interventions may differ systematically from the nonparticipants. For example, if the participants tend to be health seekers who comply with screening recommendations to a greater degree than nonparticipants, then intervention effectiveness will be overstated. Likewise, if participating providers are more likely to order screening than those refusing to participate, the results will be an overestimate of true effectiveness. Additionally, the studies identified and included were based on a review of the published literature. Studies with negative or null findings might be less likely to be published and thus less likely to be included in this review. This would result in an overstatement of the effectiveness of interventions to improve rates of mammography screening.

Finally, the long-term effectiveness of these interventions in increasing rates of regular mammography is only rarely reported (22, 26, 30, 89). Improvements in mammography utilization at a single point in time as described in the studies here do not translate directly into reductions in morbidity and mortality from breast cancer. Women must obtain screening annually (90). Even if women do receive regular screening, reductions in morbidity and mortality may not be realized as a result of delays in follow-up after an abnormal test result, incomplete diagnostic work-up, or the lack of adherence to a treatment regimen. Additionally, there may be adverse effects associated with interventions to increase mammography utilization such as increased rates of false positive exams, which are estimated to be as high as 30% among women receiving regular mammography over a 10-year period (91), and associated psychological distress (92).

Overall, all interventions appear to be effective in increasing provider-initiated mammography utilization. The effectiveness of different types of interventions in patient subpopulations such as the elderly, minorities, or those of low income and the costs of providing these interventions are critical areas for research in decreasing the morbidity and mortality associated with breast cancer.

Appendix

The formulas used to calculate variance are shown below. For randomized controlled trials, the formula used was:

$$(P_{\text{screened intervention}} \times P_{\text{unscreened intervention}})/N_{\text{intervention}} \\ + (P_{\text{screened control}} \times P_{\text{unscreened control}})/N_{\text{control}}$$

For nonrandomized concurrently controlled studies, the formula used was:

$$(P_{\text{screened preintervention}} \times P_{\text{unscreened preintervention}})/N_{\text{preintervention}} \\ + (P_{\text{screened postintervention}} \times P_{\text{unscreened postintervention}})/N_{\text{postintervention}} \\ + (P_{\text{screened precontrol}} \times P_{\text{unscreened precontrol}})/N_{\text{precontrol}} \\ + (P_{\text{screened postcontrol}} \times P_{\text{unscreened postcontrol}})/N_{\text{postcontrol}}$$

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Interventions Targeted toward Patients to Increase Mammography Use¹

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Abstract

The objective of this study was to determine the effects of patient-based mammography screening strategies. We performed a meta-analysis and included United States studies that met the following criteria: (a) randomized or concurrent control design; (b) defined outcomes; and (c) data available for reanalysis. Interventions were classified as behavioral, cognitive, or sociological and further categorized by the type of control group (active *versus* usual care), number of interventions, and mode of intervention (interactive *versus* static). Data were combined using DerSimonian and Laird random effects models to yield summary effect sizes. A total of 63 interventions in 43 studies met the inclusion criteria. Behavioral interventions increased screening by 13.2% [95% confidence interval (CI), 4.7–21.2] compared with usual care, and by 13.0% (95% CI, 8.7–17.4) when using multiple strategies and 5.6% (95% CI, 0.6–10.6) when using a single intervention compared to active controls. Cognitive interventions using generic education strategies had little impact on screening, but those that used theory-based education (e.g., health belief model) increased rates by 23.6% (95% CI, 16.4–30.1) compared with usual care. Sociological interventions also increased screening rates. Interventions using a theoretical framework were the most effective in increasing screening rates. The ability of these interventions to increase screening among subgroups and improve rates of ongoing screening, as well as the costs of these strategies, is unknown and is an important area for future research.

Introduction

Despite evidence that regular mammography screening can reduce breast cancer mortality (1–3), many women fail to

receive mammography or adhere to recommended guidelines for routine ongoing screening. In the United States, women who do not receive regular mammography are more likely to be elderly (4–10), uninsured or underinsured (10, 11), lack a usual source of care (12–15), have lower levels of education or income (10, 16–19), be non-white, (12, 13, 20–24), be non-native English speakers (25), or have low levels of literacy (12, 26, 27).

When asked why they do not receive screening, women report that breast cancer screening tests are unnecessary in the absence of symptoms (22, 28), that they do not believe themselves to be at risk of cancer (29), or that they are concerned about inconvenience, discomfort, trouble, embarrassment, or pain (27, 30). Culturally mediated concerns about modesty or dignity as well as fatalistic attitudes toward cancer may also prevent women from seeking screening (31, 32). Lower rates of mammography utilization may also result from practical considerations; in rural areas or areas that lack mammography facilities, women are less likely to receive screening (33–35). Although one of the strongest predictors of mammography screening is physician recommendation (12, 28), compliance with such a recommendation may be complicated by distrust of the medical profession in some patient populations (12, 28).

During the past two decades, numerous studies have described interventions developed to address the aforementioned patient barriers to screening (36). However, because of the large number of different interventions, numerous mechanisms of intervention action, variability in study design, and, in some cases, small sample size, it is difficult to develop a cohesive public health approach to improving screening use, particularly in high-risk populations. In this study, we perform a critical review of well-designed patient-targeted interventions designed to increase adherence with mammography. We estimate overall effect sizes for specific types of interventions to determine the most effective strategies.

Materials and Methods

Study Selection. We used the OVID search mechanism with MEDLINE in the years 1980–1998 to identify published English language articles on interventions to increase mammography utilization. The search strategy was as follows: we used the terms “mammography” or “breast neoplasms/prevention and control” ($n = 7,074$) to identify the subset of studies focused on mammography screening. We then developed a series of terms to identify settings in which interventions could take place (e.g., “primary health care,” “gynecology,” and “family physicians”) and used the terms “health education,” “health behavior,” “patient compliance,” “patient acceptance of health care,” “attitude to health,” or “health promotion” ($n = 144,660$).

The combination of these searches yielded 600 studies. Study abstracts were reviewed for evidence of prospective follow-up with either randomized assignment to an intervention or control group or a concurrent control group. Pre/post designs without controls and uncontrolled trials were excluded. Increasing rates of mammography use in the general population over

Received 2/25/99; revised 5/27/99; accepted 6/18/99.

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¹ Supported in part by Agency for Health Care Policy and Research Grant HS 08395, Grant DAMD17-94-J-4212 from the Department of the Army, a Breast Cancer Center grant (to J. S. M.), and National Cancer Institute Grants RO1 CA72908 (to J. S. M. and K. R. Y.) and T32 CA09314-19 (to K. R. Y.). An earlier version of this work was part of a 1999 report prepared for the Institute of Medicine entitled *Access to Quality Cancer Care: Evaluating and Ensuring Equitable Services, Quality of Life, and Survival*.

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Table 2 Patient-targeted behavioral interventions

	Reference no.	Study setting	Sample size		Percentage of women screened		Effect	95% CI
			Intervention	Control	Intervention	Control		
Usual care controls	59 ^a	Community	41	43	6 (15%)	2 (5%)	10	(-2.7-22.7)
	60 ^a	University	NE ^c	NE	Pre, 40.9%	Pre, 37.3%	7.5	NE
					Post, 57%	Post, 46%		
	53 ^{b,d}	Community	44	48	32 (72.7%)	17 (35.6%)	37.1	(18.2-56.0)
	53 ^{b,d}	Community	43	48	31 (72.1%)	17 (35.6%)	36.5	(17.4-55.6)
	53 ^{b,d}	Community	43	48	19 (44.2%)	17 (35.6%)	8.6	(-11.5-28.7)
	54 ^{b,d}	Community	32	31	15 (47%)	6 (19%)	28	(5.9-50.1)
	61 ^b	Community	38	38	7 (18%)	4 (11%)	7	(-8.8-22.8)
	61 ^b	Community	38	38	11 (29%)	4 (11%)	18	(0.5-35.5)
	61 ^b	Community	37	38	16 (43%)	4 (11%)	32	(13.2-50.8)
Summary	Q = 19.3						13.2	(4.7-21.2)
Active controls, single intervention	98 ^b	University	98	130	18 (18%)	25 (19%)	-1	(-11.2-9.2)
	65 ^{b,e}	Community	329	266	56 (21.0%)	73 (27.4%)	-6	(-13.3-0.5)
	55 ^{a,d}	Community	50	50	20 (40%)	17 (34%)	6	(-12.9-24.8)
	55 ^a	Community	50	50	27 (54%)	17 (34%)	20	(0.9-39.1)
	66 ^b	Community	329	329	150 (45.6%)	154 (46.8%)	-1.2	(-8.8-6.4)
	66 ^b	Community	335	329	196 (58.5%)	154 (46.8%)	11.7	(4.5-18.9)
	67 ^b	Community	381	364	159 (42%)	100 (28%)	14	(7.9-20.1)
	67 ^b	Community	198	198	28 (14%)	23 (12%)	2	(-6.6-8.6)
	68 ^b	Community	384	424	306 (79.7%)	316 (74.5%)	5.2	(-5-11.0)
Summary	Q = 14.3						5.6	(0.6-10.6)
Active controls multiple	71 ^b	Community	343	344	250 (73%)	186 (54%)	19	(12.1-26.1)
	66 ^b	Community	334	329	206 (61.7%)	154 (46.8%)	14.9	(7.4-22.4)
	54 ^{b,d}	Community	96	91	31 (32%)	33 (36%)	-4	(-17.6-9.6)
	54 ^{b,d}	Community	92	92	44 (48%)	41 (44%)	4	(-10.0-18.4)
	69 ^b	Community	1171	1171	310 (26.5%)	187 (16.0%)	10.5	(7.2-13.8)
	97 ^b	Community	95	122	20 (21%)	16 (13%)	8.0	(-2.1-18.1)
Summary	Q = 5.6						13.0	(8.6-17.4)

^a Concurrent control group.^b Random control group.^c NE, not evaluable; Pre, preintervention; Post, postintervention.^d Intervention was performed in a population of women enrolled at receipt of mammography (intervention to increase repeat screening) and excluded from quantitative analysis.^e Excluded from quantitative analysis.

affect the size of the summary estimate, but did impact the statistical significance.

The combination of six behavioral, multiple-part interventions with active controls was homogeneous ($Q = 5.6$; Refs. 54, 66, 67, 69, 71, and 97). The combined estimate for increased mammography utilization was 13.0% (95% CI, 8.6-17.4).

Cognitive Interventions. Interventions based on theories of cognitive change typically identify patient attitudes to screening and breast cancer and provide focused educational material directed at increasing compliance with mammography. For example, under the health belief model, a woman is likely to undergo screening mammography if she believes that she is susceptible to breast cancer (perceived susceptibility), that consequences of breast cancer are severe (perceived severity), that mammography has benefits in terms of reducing the impact of breast cancer (perceived benefits), and that barriers associated with receiving a mammography are low (perceived barriers; Ref. 100).

Based on differences in the approach of the cognitive interventions, we further classified cognitive strategies into generic patient education listed in Table 3 (72-77) and theory-

based education listed in Table 4 (67, 68, 70, 74, 75, 86-90, 97).

There were seven interventions that compared generic patient education strategies to usual care. These interventions were homogeneous ($Q = 7.3$), and although several led to an increase in mammography screening (72, 73, 75, 76, 77), overall, this effect was small (1.1%) and was not significant (95% CI, -2.4 to 4.6). Sensitivity analyses did not affect this interpretation.

We divided theory-based cognitive interventions into two groups based on the type of comparison group. Interventions that used usual care controls were homogeneous ($Q = 4.1$), and compared with usual care, theory-based cognitive interventions appear to be very effective in increasing the rate of mammography utilization: overall, 23.6% more women received mammography (95% CI, 16.4-30.1; Refs. 75, 88).

We divided theory-based cognitive interventions with active controls into those that were static [delivered by letter or videotape (74, 86, 87, 89)], and those that were interactive [delivered by telephone or in person (67, 68, 70, 90, 97)]. The interventions delivered by letter or videotape were homogene-

Table 3 Patient-targeted cognitive interventions—generic patient education

Intervention used performance score to describe screening.

Reference no.	Study setting	Sample size		Percentage of women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
72 ^a	University	216	216	104 (48.1%)	97 (44.9%)	3	(-6.4-12.4)
73 ^b	Worksite	384	379	Pre, 46.9% ^c	Pre, 52.8%	4.9	(-4.9-14.7)
				Post, 62.0%	Post, 63%		
74 ^a	Community	447	440	110 (24.6%)	121 (27.5%)	-2.9	(-8.7-2.9)
74 ^a	Community	595	440	161 (27.1%)	121 (27.5%)	-0.4	(-5.9-5.1)
75 ^a	Community	75	78	55 (73%)	48 (62%)	11	(-3.7-0.26)
76 ^a	Community	NE	NE	44%	31%	13	NE
77 ^a	University	143	144	26 (18%)	31 (21%)	-3	(-12.2-6.2)
Summary	Q = 7.3					1.1	(-2.4-4.6)

^a Random control group.^b Concurrent control group.^c Pre, preintervention; Post, postintervention; NE, not evaluable.

Table 4 Patient-targeted cognitive interventions—theory-based patient education

	Reference no.	Study setting	Sample size		Percentage of women screened		Effect	95% CI
			Intervention	Control	Intervention	Control		
Usual care controls	75 ^a	Community	74	78	53 (72%)	48 (62%)	10	(-4.9-24.8)
	75 ^a	Community	73	78	64 (87%)	48 (62%)	25	(11.8-38.0)
	88 ^a	Community	141	122	53 (37.6%)	21 (17.2%)	20.4	(10.0-30.8)
	88 ^a	Community	107	122	78 (29.5%)	21 (17.2%)	22.8	(18.7-26.9)
Summary	Q = 4.1						23.6	(16.4-30.1)
Active controls-static intervention	74 ^a	Community	594	440	162 (27.3%)	121 (27.5%)	-0.2	(-5.7-5.3)
	86 ^a	Community	90	63	59 (65.9%)	35 (55.2%)	10.7	(-15.7-26.4)
	86 ^a	Community	44	63	25 (57.1%)	35 (55.2%)	1.9	(-19.1-21.0)
	87 ^a	Community	401	401	201 (50%)	225 (56%)	-6	(-12.9-0.9)
	89 ^a	Community	68	65	31 (45.3%)	22 (33.8%)	11.5	(-5.0-28.0)
Summary	Q = 6.3						0.4	(-5.4-6.2)
Active controls-interactive intervention	90 ^a	Community	870	961	567 (65.2%)	608 (63.3%)	1.9	(-2.5-6.3)
	67 ^a	Community	202	198	57 (28%)	23 (12%)	16	(8.3-23.7)
	68 ^a	Community	264	424	212 (80.3%)	316 (74.5%)	5.8	(-1.0-12.6)
	70 ^a	Community	132	131	37 (28%)	20 (15%)	13	(3.2-22.8)
	97 ^a	Community	115	122	21 (18%)	16 (13%)	5.0	(-4.2-14.2)
Summary	Q = 13.0						7.9	(2.3-13.5)

^a Random control group.

ous ($Q = 6.3$) but were ineffective, with an estimated increase in mammography utilization of less than 1% (0.4; 95% CI, -5.4 to 6.2). However, theory-based cognitive interventions delivered interactively were effective, with a combined increase in mammography utilization of 7.9% (95% CI, 2.3-13.5). Sensitivity analyses did not change the interpretation of either of these estimates (see Table 4).

Sociological Interventions. We identified nine sociological interventions to increase mammography screening (Refs. 77-80, 82-85, and 91; Table 5). These patient-targeted sociological interventions used community peers (78, 83, 91), friends (80), lay health advisors (82, 84, 85), or media representations (91) of appropriate behavior to influence screening behaviors. The studies that used interactive sociological interventions were relatively homogeneous ($Q = 19.8$; Refs. 77-80 and 82-85) and improved mammography utilization by 12.6%

(95% CI, 7.4-17.9). Sensitivity analyses had little impact on this result.

We found two patient-targeted interventions that used financial incentives to try to increase mammography utilization (92, 93). Both led to increases in mammography utilization, but we could not perform meta-analysis with two interventions.

We also identified five interventions (70, 94-97) that used both behavioral and cognitive strategies to increase mammography utilization. These interventions had variable effectiveness, ranging from little effect (70, 95, 97) to a maximum effect of 33% (94).

Discussion

In our meta-analyses of patient-targeted interventions to increase mammography utilization, we found that most interven-

Table 5 Patient-targeted sociological interventions

Reference no.	Study setting	Sample size		Percentage of women screened		Effect	95% CI
		Intervention	Control	Intervention	Control		
78 ^a	Community	370	242	144 (39%)	73 (30%)	9	(1.4–16.6)
79 ^a	Community	289	302	142 (49%)	103 (34%)	15	(7.1–22.7)
80 ^a	Community	223	237	85 (38%)	37 (16%)	22	(14.1–29.9)
91 ^{b,d}	Community	Pre, 450 ^c Post, 450	Pre, 473 Post, 473	Pre, 21.4% Post, 38.1%	Pre, 24.1% Post, 43.3%	–3.5	(–7.4–0.4)
82 ^a	Community	80	94	47 (58.7%)	45 (47.9%)	10.9	(–3.9–25.7)
83 ^a	Community	165	173	64 (39%)	33 (19%)	20.0	(10.5–29.5)
77 ^a	University	151	147	44 (29%)	31 (21%)	8.0	(–1.8–17.8)
84 ^a	Community	772	711	295 (37%)	357 (42%)	–5.0	(–9.9–0.1)
85 ^a	Community	56	57	32 (56.4%)	25 (43.6%)	12.8	(–5.5–31.1)
Summary	Q = 19.8					12.6	(7.4–17.9)

^a Random control group.^b Concurrent control group.^c Pre, preintervention; Post, postintervention.^d Excluded from quantitative analysis.

tions increased rates of screening. Behavioral interventions increased screening by 13.2% (95% CI, 4.7–21.2) compared with usual care, by 13.0% (95% CI, 8.6–17.4) when using multiple strategies, and by 5.6% (95% CI, 0.6–10.6) when using a single intervention compared with active controls. Cognitive interventions using generic education strategies had little impact on screening, but those that used theory-based education (e.g., health belief model) increased screening rates by 23.6% (95% CI, 16.4–30.1) compared with usual care. Sociological interventions also increased screening rates.

The mode of intervention delivery appears to be an important component in increasing rates of mammography utilization. In particular, multiple behavioral interventions (e.g., two reminder letters) led to improved rates of mammography utilization compared with active controls, but a single behavioral intervention had a minimal effect when compared with active controls. Similarly, theory-based cognitive interventions delivered interactively via telephone or in person led to improved rates of mammography screening compared with active controls, whereas theory-based cognitive interventions delivered through letter or videotape had little impact on mammography utilization compared to active controls. The combined sociological interventions, also delivered interactively, were very effective.

These results have important public health implications for the design and delivery of interventions to increase mammography screening. Recent national estimates indicate that 56% of women over the age of 50 years have received a screening mammogram within the past 2 years (10). With the use of theory-based behavioral interventions, this number could be increased to 73–86%, with a resultant down-staging of disease and an improvement in morbidity and mortality.

Similar to our findings, in a recent review of mailed patient reminders, Wagner (100) reported that these interventions led to increased mammography utilization when compared with no intervention or a generic letter.

The results of our meta-analyses were relatively robust. By sequentially removing each study, we could determine the independent impact of a single study on overall results. In no case did the removal of a single study have a large impact on the summarized estimate, and the interpretation of the effect changed only once.

All of the interventions reviewed here included control

groups of similar women and were grouped according to mechanism of intervention action. However, there are important differences in the women enrolled in the different types of interventions, which may affect the interpretation and comparison of these results. For example, most of the patients included in the behavioral interventions had health insurance or at least a usual source of care from which a list of potentially eligible patients could be developed (61, 62, 66, 67, 69, 70). Additionally, some studies included populations of women with high rates of previous mammography (62, 79), yet many of the patients included in the sociological interventions did not have health insurance (85, 91) or had low rates of previous mammography (82–84, 91). These health care utilization characteristics, which are associated with mammography utilization in cross-sectional studies (10–13, 15), may also affect patient responsiveness to interventions to increase screening. Thus, comparisons among interventions and adaptation of interventions to dissimilar populations should be approached cautiously. Planning of new interventions should consider existing strategies in the target population, population characteristics, and available resources for intervention delivery.

There are some methodological limitations with the meta-analysis reported here, including heterogeneity among studies that were combined, inconsistencies in the unit of analysis used to calculate intervention effectiveness, reporting of multiple interventions per study with a single control group, and the combination of multiple measures of mammography utilization. We combined data from studies conducted in dissimilar populations or environments in which mammography screening is obtained and attempted to make the groups of interventions as homogeneous as possible, yet in several cases, our measures of homogeneity were high, causing us to reject the null hypothesis that interventions were homogenous. However, sensitivity analyses for these groups indicated that there was no one study that was influencing the results. Overall, combining heterogeneous studies will produce a summary estimate that is biased toward no effect.

The majority of studies we identified randomized individual women to receive either the intervention or control condition. However, some studies randomized women by physician or practice group (63, 72, 83, 98) or retirement communities (94, 97). Additionally, related individuals, such as friends of volunteers (79), or women's groups (88) were used as a source

of subjects, and peer counselors delivered interventions to multiple women (80, 82–85). Yet these data are combined as if randomization occurred individually and all observations are independent. Women treated by the same physician, living in the same retirement community, or who received tailored interventions from the same peer counselor are likely to be more similar in terms of mammography utilization than those recruited from a random sample or those that received a standardized intervention. If analyses were to incorporate the actual unit of analysis (e.g., practice group, retirement community) or correlation among individuals, CIs would be wider, but the estimate of intervention effectiveness would remain unchanged.

The impact of including data from multiple interventions that used a single control group in our summarized estimates is also likely to result in an overstatement of intervention effectiveness via narrower CIs.

The studies included here used several mechanisms to identify mammography utilization: (a) self-report; (b) chart audit; (c) electronic claims; and (d) mammography facility records. We considered the validity of these different sources to be equivalent, although this is not necessarily the case. Self-report of mammography has been described as highly correlated with mammography use reported in patient charts or claims, but it is likely to overstate utilization (101, 102), particularly among low-income minority populations (103). However, women in intervention and control groups might be equally likely to overstate mammography utilization, so the relative estimate of mammography utilization (intervention *versus* control) is unlikely to be influenced by the reporting source.

There are some more general limitations that affect the interpretation of the meta-analyses presented here. The studies identified and included were based on a review of the published literature. Studies with negative or null findings might be less likely to be published and thus less likely to be included in this review. This would result in an overstatement of the effectiveness of interventions to improve rates of mammography screening.

Finally, improvements in mammography utilization at a single point in time as described in the studies here do not translate directly into reductions in morbidity and mortality from breast cancer. Even if women do receive regular screening, it is possible that as a result of delays in follow-up after an abnormal test result, incomplete diagnostic work-up, or the lack of adherence to a treatment regimen, a reduction in morbidity and mortality may not be realized. Additionally, there may be adverse effects associated with interventions to increase mammography utilization such as increased rates of false positive exams, which are estimated to be as high as 30% among women receiving regular mammography over a 10-year period (104), and associated psychological distress (105).

Overall, behavioral interventions, theory-based cognitive interventions, and sociological patient-targeted interventions appear to be effective in increasing mammography utilization, particularly when compared with usual care. Multiple behavioral interventions and interactive theory-based cognitive interventions are effective when compared with active controls. The long-term effectiveness of these interventions in increasing rates of regular mammography is only rarely reported (60, 77), and this will be an important area for further research. Additionally, the effectiveness of different types of interventions in patient subpopulations such as elderly, minority, or low-income women and the costs of providing these interventions are critical areas for research in decreasing the morbidity and mortality associated with breast cancer.

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Equitable Access to Cancer Services

A Review of Barriers to Quality Care

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Earlier versions of this work were prepared as part of a report for the Institute of Medicine entitled *Access to Quality Cancer Care: Evaluating and Ensuring Equitable Services, Quality of Life, and Survival*.

Supported in part by the Agency for Health Care Policy and by research grant HS 08395 (Dr. Mandelblatt) and grant DAMD17-94-J-4212 from the Department of the Army, Breast Cancer Center Grant (Drs. Mandelblatt and Kerner).

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Received December 16, 1998; revisions received April 1, 1999 and July 14, 1999; accepted July 14, 1999.

BACKGROUND. Barriers to cancer care have been documented in nearly all settings and populations; such barriers represent potentially avoidable morbidity or mortality. A conceptual framework was used to describe patient, provider, and system barriers to cancer services.

METHODS. A review of the English language literature on cancer care from 1980–1998 was conducted; key research was summarized for each domain in the conceptual model.

RESULTS. Key patient barriers are related to old age, minority race, and low socioeconomic class; the common pathways by which these sociodemographic factors appear to mediate cancer outcomes include social class and race-related or class-related attitudes. Providers are often ill-prepared to communicate the complexities of cancer care to their diverse patient populations; constraints of the medical care system also can impede the delivery of care. To the authors' knowledge the impact of the rapid growth in managed care organizations (MCOs) on access to care has yet to be evaluated fully. Although MCOs historically have provided high levels of cancer screening in healthy populations, to the authors' knowledge there are fewer data regarding outcomes for elderly and poor populations and for treatment services.

CONCLUSIONS. Additional research is needed to develop and test interventions to overcome barriers to care and evaluate the impact of the growth of managed care on access to cancer care for diverse populations. *Cancer* 1999;86:2378–90.

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KEYWORDS: cancer, quality of care, barriers, health outcomes.

Each year, millions of men and women in the United States undergo cancer screening; 1.2 million will develop cancer, and more than 550,000 will die from their disease.¹ Access to quality care can have a substantial impact on cancer outcomes. Unfortunately, problems with access to cancer services have been documented in nearly all settings and populations.

In this article, a conceptual framework was used to describe barriers to quality cancer services over the full spectrum of cancer care, from secondary prevention to end of life care, and to suggest interventions for the improvement of access to quality care and cancer outcomes.

Conceptual Framework

Access has been defined as "the timely use of affordable personal health services to achieve the best possible health outcomes."² The process of gaining access to care represents dynamic interactions of diverse individuals in their social context interfacing with health care providers who, in turn, are operating in a variety of changing and

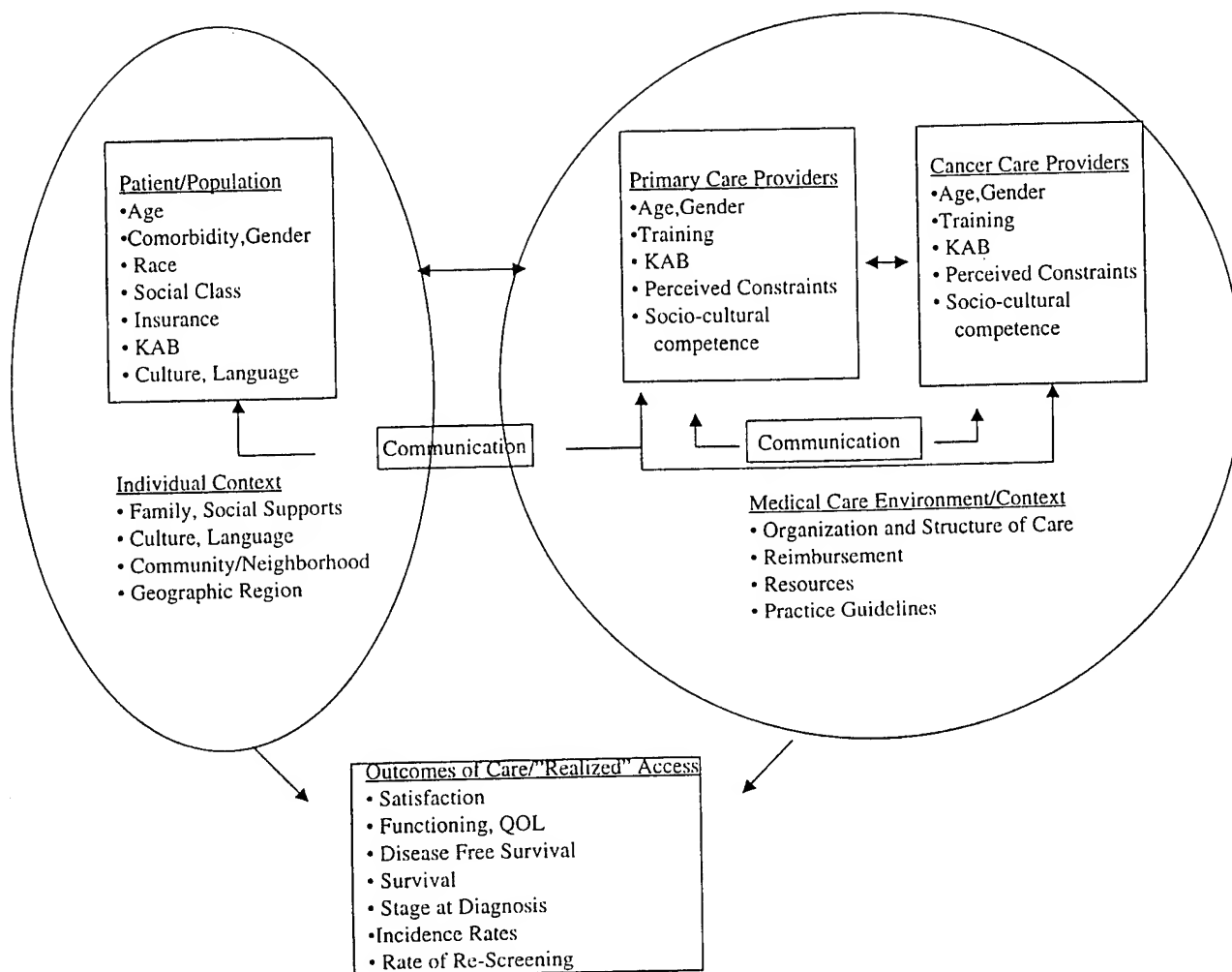


FIGURE 1. Model of access to cancer care. KAB: knowledge, attitudes, and (health) behaviors; QOL: quality of life.

often constrained medical care structures and environments. To depict this broad and interactive process, we have adapted the behavioral models of access to medical care from Andersen^{3,4} and Aday et al.⁵ to reflect access to cancer care (Fig. 1). Because primary care providers often are an important source of care for cancer patients and may be responsible for initiating orders for screening services and/or coordinating services, both primary and cancer care providers are included in the model. We have also added patient-provider and provider-provider communication as key model components.

An important component of our model was the inclusion of "realized access" to care. We have expanded the original definition of realized access from measures of utilization and satisfaction⁴ to include all outcomes of cancer care. Outcome measures are important for two reasons. First, having a quantifiable end point is necessary to determine whether access

has occurred and has had the intended effect. Second, defined outcomes are an integral part of quality measurement.⁶⁻⁸

This model can be applied to evaluating access to cancer care throughout the continuum of cancer care. First, individuals (and populations) must gain access to early detection services. Next, if a screening test is abnormal, then diagnostic services must be available. For those who are diagnosed with cancer, staging evaluation precedes and often determines treatment. Patients surviving their disease also need to have access to on-going surveillance, so that recurrences can be recognized promptly and treated. For those who will die of their disease, having access to end of life care is critical. Thus, access has different dimensions and outcomes across the spectrum of cancer care: Some domains may be more relevant for a particular phase of care but less important for others. Finally, this framework can be used as the basis for designing and

evaluating interventions addressing specific types of barriers.

BARRIERS TO CANCER CARE

The section below uses our framework to describe barriers to cancer care in each of the model domains: patients, physicians, patient-physician communication, and the health care system.

Patient Barriers

Figure 1 shows that there are many patient factors that can act as potential barriers to care, including demographics (patient age, gender, insurance, social class, race, and geography), language and acculturation, attitudes, and family and cultural contexts. Cancer is a disease of old age,⁹ yet there is limited research on barriers to cancer screening, treatment, and posttreatment care among the elderly. The potential effects of age on access to cancer care are multifaceted. First, the elderly often underestimate their risk of cancer.¹⁰ Second, along with increasing risk of cancer with age, the elderly have an average of three or more chronic medical conditions.^{11,12} The life expectancy of most elderly women (and men), however, appears to be sufficiently long to realize benefits from cancer screening,¹³ although research on the impact of comorbidity on cancer screening use and survival outcomes has been limited and inconsistent.^{12,14-22} Third, cognitive impairments, which are more frequent in elderly patients than in younger patients, also have been noted to affect cancer treatment, with the more impaired elderly patients receiving less definitive care for carcinoma of the breast and colon cancer compared with patients with lower levels of impairment.²³ Finally, the elderly are represented disproportionately in the lower social classes and have high rates of poverty, underinsurance, and out-of-pocket costs.^{24,25}

Gender effects on access are less clear. For instance, although men have lower rates of use of routine medical care in the absence of symptoms than women, affording less opportunity for opportunistic screening,^{26,27} when men do seek care, several researchers have suggested that men receive more early cancer detection tests than women in the same practices.²⁸

Beyond patient age and gender, a patient's insurance status has been noted to have a consistently strong effect on the receipt of both early cancer detection and treatment services.^{29,30} For example, patients without private insurance have been noted to receive surgery for nonsmall cell lung carcinoma less often than privately insured patients,³¹ and the rates of bone marrow transplantation for the treatment of

patients with leukemia or lymphoma are 34-50% lower for self-pay and Medicaid patients compared with privately insured patients.³²

In the past decade, Medicare has extended benefits to include cervical, breast, prostate, and colorectal cancer screening; costs of antiemetic drugs used as part of cancer chemotherapy; Group C cancer drugs (investigational drugs monitored by the National Cancer Institute); and off-label use of certain drugs for cancer therapy. However, Medicare alone has not been sufficient to remove barriers to care.^{33,34} For example, Blustein³⁴ noted that, among Medicare beneficiaries, poor women and women with no supplemental insurance were less likely to have a claim for mammography than higher income women with supplemental coverage, suggesting that copayments and deductibles represented a substantial barrier to care for disadvantaged elderly women. In 1998, Medicare eliminated copayments and deductibles for mammography and extended benefits to include annual screening.^{35,36} It will be important to confirm that the additional benefits diminish financial barriers.

Although strategies to remove economic barriers, such as providing expanded Medicare benefits, will improve access to cancer care, recent research demonstrates that this is a necessary but not sufficient condition to improve cancer outcomes.^{33,37} For instance, recent studies of cancer screening and outcomes in Canada³⁸ and Finland³⁹ demonstrate that, despite universal access to care, individuals in lower social classes persist in having lower screening and survival rates⁴⁰ compared with individuals in higher social classes.

Beyond insurance inequalities,⁴¹⁻⁴⁸ an individual's social class appears to be an important independent barrier to care. For example, regardless of the measures used and the settings examined, patients in lower social classes consistently have lower breast cancer-specific survival compared with those in higher social classes.^{48,49} Hazard ratios for survival may be as much as 60% lower for breast carcinoma patients in lower classes compared with their more economically advantaged counterparts.⁵⁰ A similar pattern is observed for patients with multiple myeloma,⁵¹ lung carcinoma, and prostate carcinoma.⁵²

For some cancers, the observed survival disadvantage may be attributable largely to the use of screening and the disease stage at the time diagnosis, in which patients in lower classes are more likely to have their disease diagnosed at advanced stages compared with their more advantaged counterparts.^{1,28,52-55} For instance, women in lower social classes are more likely to report lower use of mammography and present at later stages of breast carcinoma than their more so-

cioeconomically advantaged counterparts.^{52,55} Patient delay in reporting symptoms does not appear to have a major effect on survival for individuals in lower social classes,^{50,56,57} although others have suggested that delay leads to poorer survival, largely mediated thorough stage differences at diagnosis.⁵⁸ However, even within stages of breast carcinoma, there are social class differences in survival,⁵⁹ suggesting that adequacy of staging evaluation (Lash and Silliman, personal communication), access to timely treatment, and host factors also may contribute to the observed class disparities in survival.⁶⁰⁻⁶² Regardless of the treatment received, when cancer progresses, social class influences access to palliative and supportive care, with patients in lower classes reporting poorer symptom control and lower use of hospice care compared with patients in higher classes.⁶³

Although poorer cancer outcomes frequently are associated with nonwhite race,^{52,53} disentangling the effects of social class and race on patient outcome is complicated.^{64,65} For example, research on disease stage at the time of diagnosis,⁶⁶ rates of breast-conserving surgery⁶⁷ or other treatments, and breast cancer^{68,69} and prostate cancer⁷⁰ survival rates has demonstrated that race effects decrease or disappear after considering income or education. Another confounder of race and social class effects on access is insurance status, with minorities represented disproportionately among the uninsured or underinsured: Thirty-five percent of Hispanics and 25% of blacks report being uninsured compared with <10% of whites.⁷¹

Individual characteristics, such as race and ethnicity, are not inherently barriers to cancer care.⁷² Race is a composite term encompassing historic, biologic, sociocultural, and environmental factors, including exposure to racism.^{4,73,74} Thus, minority status may compromise access through cultural attitudes and perceptions of the care system or poverty. For instance, some Latino^{75,76} and African-American⁷⁷ populations have been noted to hold certain fatalistic attitudes toward cancer or to focus on day-to-day survival to the exclusion of seeking needed early detection or treatment care.^{27,73,78-81}

Such perspectives are likely to contribute to the observations that the rates of use of mammography, including regular use, by African-American and Hispanic women remain significantly lower than rates among nonminority women.⁸²⁻⁸⁹ Hispanic women report the lowest rates of Papanicolaou (Pap) smears or mammograms,^{87,90-93} although racial gaps in rates of recent screening may be diminishing.⁹⁴ Once African-American women and other minority women are screened, if they have an abnormal result, then as

many as 30-50% do not receive timely (or any) diagnostic resolution.⁹⁵⁻⁹⁸

When African-American patients and other minority patients are diagnosed with cancer, even after considering social class, they are more likely to be diagnosed at advanced stages of disease than whites;^{28,52,96,99,100} for cervical carcinoma, this racial gap has increased over time despite greater use of Pap smears among African-American women compared with white women.¹⁰⁰

African-American patients and older minority patients also have been observed to receive suboptimal cancer treatment^{62,101-114} and to have lower survival rates when controlling for treatment, disease stage, tumor characteristics, and/or molecular markers of prognosis.^{52,98,115-124} For instance, black women have been noted to receive definitive local or systemic treatment for breast carcinoma less often than white women,^{101,111} and black men also have been observed to receive less intensive treatment for bladder or prostate carcinoma¹⁰⁸ and have higher prostate carcinoma recurrence¹²⁵ and death rates¹²⁶ compared with white men after considering other potential confounding variables. Furthermore, a recent Institute of Medicine report concluded that minorities still are under-represented in clinical research.¹¹⁴

Another group of patient barriers to cancer services includes the distrust of health care profession,^{87,127} lower levels of health literacy, language and cultural barriers, and fears and misconceptions about cancer.^{62,75,76,87,101-105,128-142} For instance, in a study of men with prostate carcinoma, black men were more likely to have metastatic disease at diagnosis. When lower levels of health literacy were considered, as measured by items such as comprehension of medication directions, race was no longer a predictor of disease stage at diagnosis.¹⁴¹

Beliefs that religious faith is an alternative to medical care also can act as a barrier to needed care.²⁷ Cultural beliefs also have been suggested as an additional mediator for poor race-related cancer outcomes. In a seminal article, Lannin and colleagues¹⁴² examined the predictors of a later disease stage at diagnosis for women with breast carcinoma. African-American race was associated significantly with having later disease stages at diagnosis (odds ratio [OR], 3.0; 95% confidence interval [95% CI], 1.9-4.7), although this effect diminished after controlling for socioeconomic status (OR, 1.8; 95% CI, 1.1-3.2). Most striking was the finding that, after considering cultural beliefs (such as folk beliefs, religious beliefs, relationships with men, fatalism, beliefs about treatment, and knowledge), the race effect was no longer significant (OR, 1.2; 95% CI, 0.6-2.5).¹⁴² Another explanation for

the findings by Lannin et al. is that black patients and other minorities experience unique barriers, such as discrimination when seeking care, that affect attitudes.^{28,143-145}

Across all patient groups, knowledge deficits, negative attitudes, and erroneous beliefs about cancer can act as additional barriers to access to early cancer detection or treatment services.^{54,146-154} For instance, beliefs that "nothing is wrong" if there are no symptoms also can be barriers to screening^{85,155} and, when abnormal results are noted, to compliance with follow-up recommendations.¹⁵⁶ In one study, women without symptoms were more likely to fail to follow up on an abnormal mammogram than women who had a palpable mass or other symptoms.¹⁵⁶ Even when symptoms are present, many individuals state that they prefer not to know whether they have cancer.¹

In addition to the patient demographic factors and attributes and beliefs depicted in Figure 1, our model posits that the social, economic, cultural context of family, neighborhood, and geographic locale also influence how individuals perceive symptoms and seek (or do not seek) health care and what resources will be available when they do pursue care.^{27,54,158-164} For instance, despite diminished access to cancer care, an individual from a lower social class group may live in a cultural context, such as Seventh Day Adventist, that promotes healthy behaviors, which, in turn, decrease the risk of cancer occurrence and poor cancer outcomes.⁷³ In contrast, living in a socioeconomically deprived area with high unemployment and crime¹⁶⁵ also can lead to a life view focused on day-to-day survival and can lead to lower cancer screening or later disease stages of breast, cervical, or colorectal carcinoma at diagnosis.^{28,53} Area resources also can affect access. For instance, Mandelblatt and colleagues⁶⁶ noted that living in a neighborhood with a high mammography capacity increased the odds of being diagnosed with local diseases compared with living in an area with a low mammography capacity.

Primary Care and Cancer Care Providers

In our conceptual framework (Fig. 1), in addition to patient factors, health care providers play a pivotal role in ensuring access to cancer care for their patient populations. In the section below, we briefly review several physician-related barriers to care. Because primary care and oncology providers generally face similar barriers to providing cancer care in their respective practices, and because there is a paucity of research on barriers specific to oncology practitioners, we summarize barriers for both groups.

Provider recommendations are one of the most con-

sistent predictors of receipt of cancer early detection and other services.^{19,54,87,88,130,166-170} However, investigators report several barriers to providing such services, including biases and beliefs about screening and treatment efficacy, deficient knowledge and training,¹⁷¹ lack of culturally sensitive resources,^{27,72,91,172} lack of time and forgetfulness,^{173,174} concern with patient's acute illnesses, lack of confidence (e.g., in clinical breast examination [CBE] proficiency),¹⁷⁵⁻¹⁷⁷ confusion about conflicting professional recommendations on standards of care,^{173,178,179} concerns about patient acceptance,^{173,180,181} lack of reimbursement or cost concerns,^{65,69,174,177,180-182} and logistic or organizational barriers.^{173-175,183} Physicians also may hold age or race biases. For instance, many studies have noted that physicians order mammography screening less often for elderly patients compared with younger patients.¹⁸⁴⁻¹⁸⁸ Providers also tend to order fewer intensive diagnostic work-ups¹⁸⁹ and offer definitive primary^{23,102,105,190-195} and adjuvant cancer treatment less often,^{103,104,106,111} including bone marrow transplantation¹⁹⁶ and radiation or chemotherapy after breast conservation,^{105,106} among elderly patients compared with younger patients. Beyond age biases, these patterns in management of the elderly may reflect the need to tailor therapy based on comorbidity, concerns about treatment toxicity, or differences in expectations of outcome among elderly patients and their physicians.

Subtle race biases of physicians also have been suggested as an explanation for the undertreatment of certain patient groups.¹¹¹ For example, several researchers have noted that physicians are more likely to order cancer screening for their white patients than for their nonwhite patients.^{87,88,112,128}

Physician characteristics, such as male gender,^{138,171,175,197} older age,^{171,198} white race,^{199,200} specialty practice,^{167,171,184,186,198,201-207} and a greater number of years since graduation²⁰³ all have been noted to constitute additional potential barriers to optimal cancer screening and treatment services. For instance, male physicians often perform cervical cancer screening less often than female physicians,¹³⁸ and they see patients for health maintenance visits less frequently than female physicians.²⁰⁷ Other examples include specialists who, when providing primary care, omit cancer screening more frequently than primary care providers.^{174,177}

Finally, as depicted in our conceptual framework (Fig. 1), physician-patient communication is another key domain in determining access to care. The quality of physician communication about cancer care has been noted to vary by physician gender,²⁰⁸⁻²¹² by patient race or ethnicity,^{87,209,211,213} and by patient social class.²¹⁴ For example, physicians discuss mammogra-

phy less often with their Hispanic patients than with their non-Hispanic patients, and Black patients are less likely to report advice about cancer screening than whites who see the same physician.¹²⁷ This will be an important area for further study and intervention.

Medical Cancer Care Environment

The last domain in our model represents attributes of the health care system within which patients and providers operate. Beyond specific patient or physician factors, system attributes can either facilitate or hinder obtaining needed care for cancer services (Fig. 1). Potential system barriers include organizational and structural factors, reimbursement and financial forces, quality measurement, and regional resources.

Over the past decade, hospitals and other health care systems have experienced unprecedented financial constraints with high rates of closings, relocations, mergers, and development of for-profit models.²⁹ The loss of care resulting from such closures or restructuring of financial eligibility requirements has been noted to have a strong adverse effect on chronic disease health outcomes, ranging from hypertensive control to avoidable mortality.^{183,215-217} The effects on cancer care are likely to parallel these trends.

In the same time period, another dramatic change in the structure of the health care system has been the rapidly increasing proportion of the U.S. population enrolled in managed care organizations.²¹⁸ However, there are few data available on how the structure and financing of managed care organizations affect access to and outcomes of cancer care.^{124,219-225} Although prior research demonstrates that managed care settings deliver more early cancer detection services than fee-for-service practices, even after attempting to account for self-selection factors,^{167,226,227} it is not clear whether patients of lower social classes, minorities, and elderly persons more recently enrolled in Medicaid or Medicare managed care will realize similar advantages.^{72,228} Once a patient develops cancer, the effects of the setting of care are conflicting. For instance, Lee-Feldstein and colleagues²²⁹ found that women who underwent treatment for local stage breast carcinoma in health maintenance organization (HMO) hospitals had poorer survival when controlling for patient age, tumor size, lymph node status, and histologic type compared with women who underwent treatment in large community and teaching hospitals.²²⁹ In contrast, Potosky and colleagues²²⁴ failed to find such an effect in two geographic settings; in fact, in one setting, women who were treated in HMOs had better survival compared with women who were treated in other settings.

The selection of physicians into managed care also may influence access to services. In a recent population-based study of California physicians, Bindman and colleagues²³⁰ found that physicians who cared for a larger percentage of uninsured and nonwhite patients were significantly less likely to have managed care contracts. Thus, the correlation between the organization and financing of care and cancer processes and outcomes are far from clear at this point and may be changing over time as the managed care market matures.

Other structural aspects of care, including hospital type and size, teaching status,^{110,231} and availability of radiation therapy,¹⁹⁴ influence access to care and the type of care received. For instance, women with local breast carcinoma who receive care in teaching hospital settings are more likely to receive breast conservation than women who receive care in nonteaching settings.^{110,223,232} Patients who are seen in larger practices also are more likely to be seen for health maintenance visits.²⁰⁷ Within a given health care structure, inadequate tracking mechanisms (e.g., identification of patients who miss appointments for screening, follow-up, or episodes of treatment) also can constitute a barrier to care.²³³

Regardless of the organization of care, the structure and process of primary and specialty care also can act to facilitate or impede the receipt of cancer services. For instance, among women with a regular source of care, Bindman and colleagues¹⁶⁹ noted that several features of optimal primary care, including availability of care, continuity, comprehensiveness, and communication, were related significantly to the receipt of breast and cervical cancer screening independent of insurance status, patient sociodemographics, and chronic disease history.

Financial structure and reimbursement variability also can act as barriers to cancer care. For example, in the fee-for-service sector, Medicare and Medicaid often reimburse providers less than private insurers for similar services,²³⁴ potentially acting to discourage providers or institutions from accepting patients with public insurance. Managed care capitation rates or financial incentives also may influence provider behavior if provision of extensive cancer services may result in a loss of income. The higher relative reimbursement for performing invasive procedures compared with providing patient counseling may act as a barrier to patient-physician communication.

Neighborhood health care resources, such as the number of mammography facilities per female population⁵² or HMO market share,²³⁵ have been noted to influence breast cancer stage at diagnosis or screening patterns. Finally, men and women in rural areas also

may be less likely to receive cancer screening or state-of-the-art treatment as a result of inadequate resources, long distances to sites of care, or transportation problems.²³⁶⁻²³⁸ For instance, regional variations in access to care have been noted, including differences in access to surgical treatment, for patients with breast carcinoma^{10,193,239-241} and prostate carcinoma.¹⁰⁸ The rates of use of systemic chemotherapy also show geographic variations, with patients in rural areas receiving less systemic treatment than those living in more urban locations.²⁴⁰

CONCLUSIONS

There are pervasive patient, physician, and health care system barriers to accessing quality cancer care. The central barriers that act at the patient level include low social class, minority status, and patient age; class and culturally mediated attitudes may be key final pathways that mediate the disproportionately poor cancer outcomes observed in these vulnerable population groups. At the physician level, gaps in training in patient-physician communication constitute an unaddressed barrier to cancer care. The growth of managed care represents the major potential system barrier or facilitator to better access to care: It remains to be seen which of these will result.

Many interventions to improve access to cancer services have been developed targeting one or more of the domains portrayed in our model of access to care. The majority of interventions focus on patient barriers to breast and cervical cancer screening. For instance, educational strategies based on a theoretical framework, such as the precede-proceed or predisposing, enabling, and reinforcing models of behavior, have been used successfully to overcome low patient knowledge or attitudinal barriers and to increase mammography screening rates.²⁴² Similarly, interventions targeted to physicians that rely on behavioral cues (e.g., reminders) and education have been used to increase breast cancer screening rates.²⁴³ There are few interventions that specifically target the elderly²⁴⁴⁻²⁴⁶ or racial minorities²⁴⁶⁻²⁴⁹ or that evaluate methods for improving colorectal cancer screening.^{250,251} To date, there also is a paucity of research on patient-based or physician-based interventions focused on cancer treatment or posttreatment care and fewer still that involve the medical care system. Interventions designed to enhance access also will need to be evaluated systematically to ensure that patient outcomes are improved in the most cost-efficient manner. Together, future interventions hold the promise of eliminating the current inequalities in access to cancer care in the United States.

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Patterns of Breast Carcinoma Treatment in Older Women

Patient Preference and Clinical and Physician Influences

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BACKGROUND. Older women have high rates of breast carcinoma, and there are substantial variations in the patterns of care for this population group.

METHODS. The authors studied 718 breast carcinoma patients age 67 years and older who were diagnosed with localized disease between 1995 and 1997 from 29

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Supported by Grant No. R01 HS 08395 from the Agency for Health Care Policy and Research and Grant No. DAMD17-94-J-4212 from the Department of the Army.

The authors thank the women who shared their breast cancer stories with them, Lynne Eggert, M.P.H., Project Coordinator for field implementation of the protocol, the OPTIONS support staff who made data collection possible, Yi-Ting Hwang, Ph.D., for biostatistical support, Mathematica Policy Research, Inc. for data management and collection, Mary Cummings, Ph.D., for programmatic support, the OPTIONS National Advisory Committee for helpful suggestions on the conduct of the project, Ms. Sandy Fournier for administrative support, and Ms. Kathy Summers for manuscript preparation.

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Received April 6, 2000; accepted April 6, 2000.

hospitals in 5 regions. Data were collected from patients, charts, and surgeons. Logistic regression analysis was used to evaluate determinants of treatment.

RESULTS. Women who were concerned about body image were 1.8 times more likely (95% confidence interval [95% CI], 1.1–2.8) to receive breast conservation surgery and radiotherapy than women without this preference, controlling for other factors. In contrast, women who preferred receiving no therapy beyond surgery were 3.9 times more likely (95% CI, 2.9–6.1) to undergo mastectomy than other women, after considering other factors. Radiotherapy was omitted after breast conservation 3.4 times more often (95% CI, 2.0–5.6) among women age 80 years and older than among women ages 67–79 years, controlling for covariates. Black women tended to have radiotherapy omitted after breast conservation surgery 2.0 times more often (95% CI, 0.9–4.4) than white women ($P = 0.09$). Women age 80 years and older also were 70% less likely (odds ratio = 0.3; 95% CI, 0.1–0.8) to receive chemotherapy than women ages 67–79 years, controlling for health, functional status, and other covariates.

CONCLUSIONS. After considering other factors, patient preferences and age were found to be associated with breast carcinoma treatment patterns in older women. Further research and training are needed to provide care for the growing population of older women that is both clinically appropriate and consonant with a woman's preferences. *Cancer* 2000;89:561–73. © 2000 American Cancer Society.

KEYWORDS: breast carcinoma, elderly, treatment, patterns of care.

Breast cancer is largely a disease of old age. Currently, nearly 50% of the new cases and nearly two-thirds of the deaths from this disease occur among the 13% of the female population that is age 65 years or older.^{1,2} Based on the survival equivalence of two treatment approaches—mastectomy and breast conservation—breast conservation and radiation therapy often is recommended for the treatment of localized disease.³ Although the clinical trials that served as the basis for this recommendation did not include many women ages 65 years or older, there are no specific contraindications to breast conservation in this age group. After several years of low rates of breast conservation among older women,^{4–8} rates started increasing in the mid-1990s⁹ and now approach those observed for younger women.¹⁰

However, within the older age group, the oldest women appear to be receiving less breast conservation, and when they do get breast conservation, they are receiving radiotherapy less often than others.^{4–6,11–18} There are several possible explanations for such patterns of care, including underlying health,^{19,20} day-to-day ability to function,²¹ age and/or socioeconomic biases,^{4,7,15,22} psychologic factors and patient preferences for treatment,^{23–25} geographic variations or access barriers,^{4,5,7,15,26–31} and physician attitudes toward treatment and patient involvement in treatment decisions.^{13,21,32–35} Previous research has produced inconsistent results for one or more of these factors,^{8,19,20,36} has not included data on disease stage,³¹ or has not collected sufficiently

detailed information to understand the role of age on treatment patterns within the older age group.

In this article, we present results from a prospective cohort of newly diagnosed older women with localized breast carcinoma. We evaluate the independent effects of patient, clinical, surgeon, regional, and other factors on the receipt of primary surgical and adjuvant therapy. We hypothesize that: 1) after considering preferences, stage, physical function, and comorbidity, age will be associated with surgical treatment, and that when breast conservation is used, age will be inversely related to receipt of radiation therapy; and 2) that age also will be associated with receipt of systemic adjuvant treatment, controlling for tumor characteristics and other factors.

METHODS

This study uses data from the institutional review board approved breast cancer Outcomes and Preferences for Treatment in Older Women Nationwide Study (OPTIONS) project.

Setting and Population

Between November 1, 1995 and September 30, 1997, older women with breast carcinoma were ascertained weekly from inpatient and outpatient pathology records and surgical logs at a convenience sample of hospitals ($n = 29$) in Massachusetts, Texas, Washington, DC, Western New York State, and New York City. This convenience sample was used to develop an un-

derstanding of the mechanisms underlying observed treatment patterns; hospitals were selected based on the availability of a collaborating investigator and having a large number of elderly breast carcinoma patients. The 29 hospitals included 3 (10.3%) National Cancer Institute designated comprehensive cancer centers; 20 of the 29 (69%) had surgery programs accredited by the American College of Surgeons. Based on a review of tumor registry data for a subsample of sites, case ascertainment appeared to be complete.

Women were considered eligible if they were community dwelling, 67 years of age or older, and had histologically confirmed primary T1 or T2; N0, N1, or NX; M0 invasive breast carcinoma. Women with ductal carcinoma in situ, bilateral carcinoma, or multicentricity were excluded, because breast conservation and mastectomy may not have been considered "equivalent" choices for these women. The younger age limit reflects the fact that elderly women were required to have 2 years of Medicare claims before cancer diagnosis for inclusion in the study; there was no upper age limit. Figure 1 summarizes the sample selection. Based on pathology reports, 1932 potentially eligible women were identified; 555 of these women subsequently were found to be ineligible. Reasons for ineligibility included history of prior breast carcinoma, having a second primary breast carcinoma, or having nonlocal or unknown stage (47%), moderate to severe cognitive impairment (9%), visual, hearing, or severe physical impairments (8%), being non-English speaking (9%), administrative delays (8%), and other administrative issues unrelated to the project (e.g., loss of staff) (12%), residence in a nursing home (4%), and death within 3 months of diagnosis (3%). Among the remaining 1377 eligible women, physician consent to contact 84% (n = 1159) was obtained.

Eligible women were sent printed materials introducing the study. Using a standard protocol, women then were contacted up to 10 times at different times of the day, 7 days a week before being considered a nonrespondent. Of the 1159 women invited to participate, 67.6% consented and completed interviews (n = 784). Sixty-six women were found to be ineligible after interviews were completed (due to incomplete stage or treatment data, nonlocal stage, or history of prior or second primary breast carcinoma), yielding 718 women in the final study population. We were not allowed to obtain any demographic information on women whose physicians refused for them, or who themselves refused to participate. Based on available data, the rates of eligibility, physician consent, and patient consent were similar across the 5 geographic regions, with 1 exception; rates of patient consent were lower in New York City than overall (59% vs. 68%;

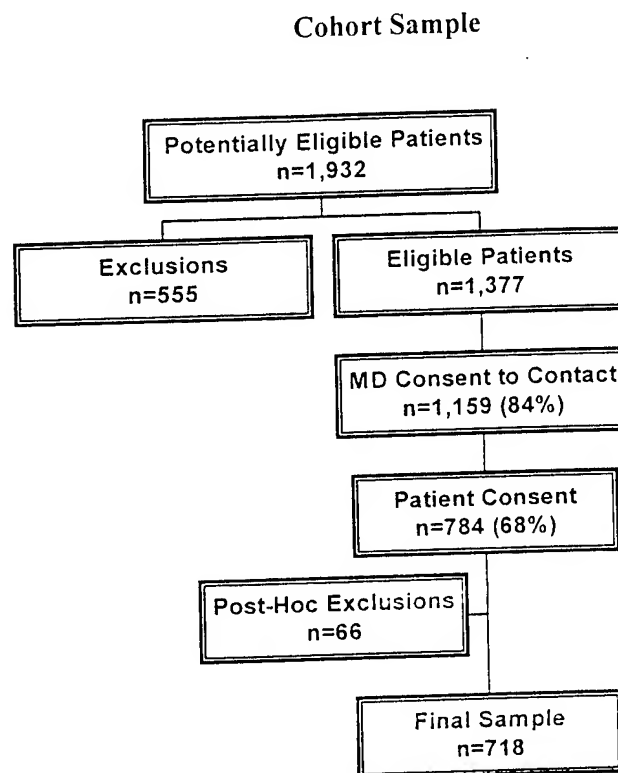


FIGURE 1. Eligibility criteria for the cohort sample are shown. Eligibility criteria included age 67 years old or older; histologically confirmed primary T₁ or T₂; N₀, N₁, or N_x; M₀ invasive breast carcinoma. Exclusions included bilateral carcinoma or multicentricity, prior breast carcinoma, having a second primary breast carcinoma, or having nonlocal or unknown stage (47%), moderate to severe cognitive impairment (9%), visual, hearing, or severe physical impairments (8%), being non-English speaking (9%), administrative delays (8%), and other administrative issues unrelated to the project (e.g., loss of staff) (12%), residence in a nursing home (4%), and death within 3 months of diagnosis (3%). Physician (MD) consent was required before contacting women for participation. Post hoc exclusions included: nonlocal stage, history of prior breast carcinoma, or second primary breast carcinoma noted after patient interview, incomplete stage, or treatment data.

$P < 0.05$). The group of nonparticipants (based on physician refusal or patient refusal) and excluded women were of similar ages as the final participants (75.0 years vs. 75.2 years).

Data Collection

Data were collected from three sources: patient interviews, surveys of their surgeons, and medical records.

Patient Interview

Women were contacted by trained staff between 6 and 24 weeks (mean, 18 weeks) after surgery for completion of a 1-hour in-person interview: 71.7% of the interviews were completed in person and 28.3% over

the telephone. The structured interview focused on sociodemographic factors (marital status, living arrangements, and insurance), health status (posttreatment social, role, emotional, physical, and sexual functioning, and pretreatment physical function and cardiopulmonary symptoms), preferences considered in making treatment decisions, and perceptions of having a choice of therapy.

Medical Record Abstraction

Data were recorded from charts using a structured tool, including all procedures and treatments, tumor grade, hormone receptors, staging, and referrals made.

Physician Survey

Surgeons were asked to complete a 15-minute self-administered survey to ascertain demographic and practice characteristics and attitudes toward patient participation in treatment decision making. Volume of practice was determined by asking: "what proportion of your breast cancer patients treated in 1994 were 65 years or older?" Usual practice was measured by asking: "Among your patients in your practice 65 and over with T1/T2 breast cancer, and nodal [lymph node] status N0/N1 (either clinical or pathologic) observed in 1994, what percentage received breast conservation? Mastectomy?" Attitudes toward patient participation were measured using a previously validated 11-item scale.^{33,34} The survey was completed by 138 surgeons (71%) who had 613 patients in the final sample; matching surgeon data were missing for 105 patients.

Definition of Variables

The main dependent variable for this analysis was the local treatment received as noted in the medical record: breast conservation with radiotherapy, breast conservation alone, or modified radical mastectomy. Breast conservation was defined as excisional biopsy (with no follow-up procedures), lumpectomy, partial or segmental mastectomy, tylectomy, quadrantectomy, and wedge resection. Mastectomy included subcutaneous mastectomy, modified radical mastectomy, and total mastectomy. If a woman initially had breast conservation, but had involved margins not cleared by reexcision, and eventually received mastectomy, then she was coded as receiving mastectomy.

The secondary outcomes were defined using medical record and patient interview data and included systemic therapy received: tamoxifen use (yes/no) and chemotherapy (any chemotherapy yes/no). Adjuvant therapy also was defined as treatment that was consistent with the 1995 St. Gallens consensus recom-

mendations for the elderly for 3 levels of risk: low risk (tumors < 1 cm, estrogen receptor [ER] positive, and Grade 1): tamoxifen; intermediate risk (1–2-cm tumors, Grade 1 or 2, and ER positive): tamoxifen and/or chemotherapy; and high risk (tumors > 2 cm, Grade 3, or ER negative): chemotherapy.³⁷ The concordance between patient report and medical records for surgery, radiation, and tamoxifen and chemotherapy use was excellent (95%); discordant cases were reviewed and sites were queried to resolve any discrepancies.

Patient Level Predictors

Patient predictors of treatment included age, comorbidity and functional status, sociodemographics, and preferences. Because preliminary analyses demonstrated that the important age-related differences in treatment occurred for women older and younger than age 80 years (data not shown), age was grouped into 2 categories: 67–79 and 80+ years.

After examining a number of approaches to measuring comorbidity,³⁸ we used a count of the number of illnesses in the 2 months before diagnosis. The number of illness was based on the Index of Coexistent Diseases (ICED) from the medical records and patient reports. The ICED has been used to predict breast carcinoma treatment and includes 14 categories of illness and a measure of the severity of each.¹⁹ Patients also were asked about selected conditions felt to impact on treatment decisions, including cardiopulmonary disease, diabetes, and neurologic conditions, by using 14 items from the Total Illness Burden Index.²¹ Functioning in the 2 months before cancer diagnosis was measured using the 10-item Medical Outcomes Study Short Form 36 physical function scale (Cronbach alpha, 0.93).

Sociodemographic factors were defined as categorical level variables: white versus nonwhite, lower than high school education versus high school education and higher, health maintenance organization (HMO) enrollment (yes/no), and supplemental private insurance (private Medigap) versus other insurance.

Women's preferences in making treatment decisions were categorized as yes, "this was a concern for me in making my (surgical) treatment decision" or no, "it was not a concern in making my (surgical) treatment decision" (e.g., appearance, wanting to get treatment over with, not wanting anything except surgery, chance of the cancer coming back, family preferences, concern about costs, inconvenience of treatment, and concern about side effects). Perception of having a treatment choice was assessed in a yes/no format. Difficulty with transportation to medical care (yes/no) also was evaluated.

Clinical Disease Factors

Stage was categorized as Stage I, IIA, and IIB: 68.2% were staged based on pathology, and the remainder were staged on a combination of pathologic and clinical data. Estrogen and progesterone receptors were considered to be positive, negative, or unknown. Grade included 1, 2, 3, and unknown. Referrals to a medical oncologist or radiation oncologist were coded as yes or no.

Surgeon Factors

We evaluated surgeons' characteristics, including surgeon age, gender, training (surgical oncology vs. not), and self-reported percentage of practice devoted to breast carcinoma, and percentage of surgery among the elderly that was breast conserving. Physicians' attitudes toward patient participation in decision making was treated as a continuous variable, based on a scale score ranging from 11 to 55, with higher scores indicating a greater endorsement of patient participation.^{33,34} Among these surgeon variables, self-reported percentage of surgery among the elderly that was breast conserving was the strongest predictor of treatment and is used in subsequent analyses.

Other Factors

The last set of variables controlled for other factors that might affect treatment, including geographic location, cancer center (yes/no), and year of surgery (1995, 1996, or 1997).

Analysis

Bivariate relations between individual variables and treatment received were examined using *t* tests (two-sided), one-way analysis of variance, and chi-square statistics.³⁹ Missing data (< 10% for any variable) were not related to treatment and were imputed as follows: for continuous variables, the mean was assigned; for categorical variables, missing was assumed to be equivalent to not having the variable. Logistic regression models then were constructed entering all variables that were significant in bivariate analyses ($P < 0.05$), were controlling variables, and/or relevant to the hypothesis (i.e., a priori specification, not stepwise). Controlling variables (age, stage, race, education, insurance and HMO, health, and region and site of care) were retained in the models regardless of significance level; other nonsignificant variables were removed from the final models to derive the most parsimonious model. Each local therapy logistic model examined one treatment compared with all other treatments. Three systemic therapy models were developed—one each for tamoxifen (yes/no), chemotherapy (yes/no),

and adjuvant therapy consistent with the St. Gallen's recommendations (yes/no). Model fit was assessed by the C statistic.⁴⁰

RESULTS

Characteristics of the women are presented in Table 1. Table 2 includes patient characteristics stratified by age (67–79 vs. 80+ years). Women 80 and older were less likely than women 67–79 years to have been referred to a radiation oncologist (28% vs. 44%; $P = 0.001$). Overall, half of the women receiving breast conservation alone were referred to a radiation oncologist; 55.2% younger than 80 years and 38% for women 80 years and older ($P = 0.05$), suggesting that either patient or physician compliance or agreement with recommendations may influence treatment received.

Determinants of Local Therapy

Consistent with expectations, being referred to a radiation oncologist was the strongest independent predictor of treatment, in which women who were referred were 20 times (95% CI, 2.3–32.8) more likely to have breast conservation and radiation than other treatments, compared with women who were not referred. As hypothesized, women 80 years and older were 3.4 times (95% CI, 2.0–5.6) more likely than younger women to have radiation omitted after breast conservation, compared with other treatments, controlling for health, preferences, and other variables (Table 3).

Concern about body image was independently associated with odds of breast conservation and radiotherapy that were 1.8 times greater (95% CI, 1.1–2.8) than for women without this preference. In contrast, women who stated a preference for having no therapy beyond surgery were 3.9 times (95% CI, 2.9–6.1) more likely to receive mastectomy than other women, after considering other factors.

There were also regional differences in treatment, with women in Texas receiving mastectomy 3.3 times (95% CI, 1.6–6.5) more often than other treatments than women in Massachusetts. Finally, Black women were 2.0 times (95% CI, 0.9–4.4) more likely to have radiotherapy omitted after breast conservation than white women, although this effect did not reach statistical significance in this small sample of blacks ($P = 0.09$).

Adjuvant Systemic Therapy

Age was inversely related to receipt of chemotherapy, after considering health, clinical, and other factors, but women 80 and older tended to receive tamoxifen more often than women 67–69 years old (odds ratio

TABLE 1
Characteristics of the Cohort by Local Treatment

Characteristic	No.	Local treatment		
		Breast conservation and radiotherapy (%)	Breast conservation only (%)	Mastectomy (%)
Overall	718	50	13	37
Age ^a (yrs)				
67-79	568	56	10	34
80+	150	30	31	39
Stage ^a				
I	564	55	15	30
IIA	132	33	14	53
IIB	22	27	9	64
Systemic treatment ^a				
Chemotherapy only	93	26	31	43
Tamoxifen only	446	62	8	30
Both	50	0	32	68
Neither	129	57	12	31
Education ^a				
Lower than high school	330	45	18	36
High school or higher	388	55	11	34
Race ^a				
White	653	51	13	34
Black	65	42	27	31
Insurance coverage ^b				
HMO	187	55	11	34
Private	589	51	14	35
Transportation problem ^a (yes)	113	30	14	56
Not wanting any treatment after surgery ^a	150	24	16	60
Concern with appearance ^a	494	61	11	28
Concern with family preferences ^a	196	43	15	42
Wanting treatment over with ^a	196	43	22	35
Concern about chance of the cancer coming back ^a	611	51	13	36
Concern about inconvenience of getting to treatment ^a	166	40	13	47
Given choice of treatment (yes)	572	42	13	45
Treated in a cancer center	209	41	14	45
Mean prediagnosis physical function ^a (n)		76.2	62	68.9
Mean no. of Comorbidities (n)		2.1	2.6	2.7
Mean of surgeons' patients receiving BCS ^a (%)		57.8	58.6	48.5

HMO: health maintenance organization; BCS: breast-conserving surgeon.

^a $P < 0.05$.

^b Not mutually exclusive categories of insurance.

[OR], 1.97; 95% CI, 0.92-4.18) (Table 4). Women who had ER positive tumors were 4.3 (95% CI, 2.2-8.3) times more likely to receive tamoxifen than women with ER negative tumors.

Women who had radiotherapy omitted after breast conservation were 11.3 times more likely to receive chemotherapy (95% CI, 4.6-27.4), independent of other factors. However, women 80 years and older, who were the most likely to have radiation omitted, were 70% (OR, 0.3; 95% CI, 0.1-0.8) less likely to receive chemotherapy than women 67-79 years old, controlling for other factors.

To evaluate consistency of systemic treatment with consensus recommendations in place at the time

of the study, we also examined predictors of treatment consistent with those recommended at the 1995 St. Gallens conference. Age patterns of treatment persisted but were not significant, given the high use of tamoxifen in all women.

DISCUSSION

This is one of the first large studies of breast cancer treatment to focus on older women with a defined disease stage and to include detailed information about patient, clinical, physician, and other factors affecting both local and systemic treatment patterns. In our research, age was a very strong determinant of breast carcinoma treatment: women 80 and older

TABLE 2
Characteristics of the Cohort by Age and Selected Factors (n = 718)

Characteristic	Age		P value
	67-79 yrs (n = 568) (%)	80+ yrs (n = 150) (%)	
Stage			
I	79	79	
IIA	18	18	
IIB	3	3	0.99
Local treatment			
Breast			
Conservation and radiation	55	31	
Mastectomy	10	31	
Breast conservation	35	38	0.001
Had axillary lymph node dissection	75	49	0.001
Systemic treatment			
Chemotherapy	7	4	
Tamoxifen	56	61	
Both	7	1	
Neither	31	33	0.04
Positive margins	30	37	p = 0.15
Grade			
1	11	7	
2	20	23	
3	12	12	
Unknown	56	58	0.54
Estrogen receptor+	64	65	0.96
Referral to a radiation oncologist	44	28	0.001
Referral to a medical oncologist	47	40	0.15
High school education or higher	57	45	0.009
Black	8	9	0.93
Insurance coverage			
HMO	27	17	0.017
Private	82	82	0.99
Would have a transportation problem for treatment	13	27	0.001
Not wanting any prescriptions after surgery	19	27	0.05
Concern with appearance	32	27	0.25
Concern with family preferences	27	30	0.40
Wanting treatment "over with"	65	75	0.02
Concern about chance of the cancer coming back	89	79	0.001
Concern about inconvenience of treatment	20	37	0.001
Given choice of treatment	82	72	0.009
Treated in a cancer center	31	24	0.12
Mean prediagnosis physical function	75 ± 27	60 ± 31	0.05
Mean no. of Comorbidities	2.3 ± 1.6	2.7 ± 1.9	0.05
Region			
New York State	19	20	
Texas	33	32	
Washington DC	16	17	
New York City	6	5	
Massachusetts	26	26	0.99
Year			
1995	9	10	
1996	48	48	
1997	43	42	0.90
Mean Surgeons' Patients undergoing BCS ^a (%)	54 ± 19	54 ± 20	0.90

+: positive; HMO: health maintenance organization; BCS: breast-conserving surgery.

^a Surgeon self-report.

TABLE 3
Adjusted Odds of Local Treatments in Elderly Women^a

Variable	BCS and RT		BCS Alone		Mastectomy	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (yrs)						
67-79	1.00	—	1.00	—	1.00	—
80+	0.47	0.28-0.81	3.39	2.04-5.64	0.62	0.37-1.05
Stage						
I	1.00	—	1.00	—	1.00	—
IIA	0.30	0.17-0.53	0.78	0.42-1.44	3.47	2.06-5.85
IIB	0.19	0.05-0.72	0.49	0.10-2.37	6.37	1.64-24.77
No. of illnesses	0.88	0.77-1.01	1.01	0.87-1.17	1.12	0.97-1.28
Physical function ^b	1.00	1.00-1.01	0.99	0.98-1.00	1.00	0.99-1.01
Referral to a radiation oncologist						
Yes	20.07	2.29-32.78	0.39	0.22-0.67	0.05	0.03-0.09
No	1.00	—	1.00	—	1.00	—
Margins involved						
Yes	0.75	0.48-1.18	0.97	0.58-1.62	1.63	1.04-2.55
No	1.00	—	1.00	—	1.00	—
Black	0.62	0.28-1.40	1.98	0.90-4.40	0.82	0.36-1.89
Education						
Lower than high school	1.00	—	1.00	—	1.00	—
High school or higher	1.49	0.96-2.33	0.66	0.40-1.10	0.87	0.56-1.36
HMO member	1.35	0.80-2.28	0.99	0.54-1.80	0.72	0.42-1.22
Private insurance	1.79	0.99-3.25	1.03	0.54-1.96	0.52	0.29-0.94
Treated in a cancer center	0.79	0.45-1.39	0.79	0.41-1.53	1.49	0.85-2.59
Given a choice of treatment	0.88	0.52-1.46	1.44	0.79-2.62	0.80	0.48-1.34
Would have a transportation problem for treatment	0.60	0.32-1.09	0.47	0.23-0.95	2.84	1.60-5.03
Did not want treatment after surgery	0.17	0.10-0.31	1.07	0.60-1.88	3.94	2.38-6.51
Concerned with appearance	1.77	1.13-2.75	0.90	0.53-1.53	0.62	0.39-0.99
Family preferences important	0.74	0.46-1.21	1.36	0.79-2.36	1.02	0.62-1.66
Wanting treatment "over with"	1.11	0.67-1.84	0.37	0.22-0.63	1.96	1.17-3.28
Self-reported breast conservation in the elderly ^b (%)	1.01	1.00-1.02	1.01	1.00-1.03	0.98	0.97-0.99
Region						
New York State	0.44	0.22-0.89	1.10	0.52-2.32	1.97	0.95-4.06
Texas	0.41	0.21-0.81	0.63	0.29-1.41	3.27	1.64-6.54
Washington, DC	0.83	0.41-1.65	1.17	0.55-2.49	1.08	0.53-2.19
New York City	2.75	0.94-8.03	0.30	0.22-0.06	0.67	0.22-2.02
Massachusetts	1.00	—	1.00	—	1.00	—
Year of surgery						
1997	1.00	—	1.00	—	1.00	—
1996	1.65	1.05-2.57	0.61	0.36-1.02	0.81	0.51-1.28
1995	0.56	0.21-1.47	0.56	0.23-1.39	1.88	0.81-4.35
C statistic	0.90	—	0.78	—	0.89	—

BCS: breast-conserving therapy; RT: radiotherapy; OR: odds ratio; CI: confidence interval; HMO: health maintenance organization.

^a Adjusted odds ratios, in which each variable is adjusted for the effects of all other variables in the table. Predicts odds of each treatment compared with the remaining two treatments.^b Odds for each 1-point increase on a scale from 0 to 100.

were 3.4 times more likely to have radiotherapy omitted after breast conservation than women ages 67-79 years, independent of comorbid illnesses, physical functioning, or women's treatment preferences. Age differences in surgical treatment extended to use of adjuvant therapy, with women 80 and older receiving chemotherapy 70% less often than women 67-79 years

with similar tumor characteristics and health, but tending to be twice as likely to have received tamoxifen as the younger age group.

These data lend support to our hypothesis of potential age biases in breast carcinoma treatment and are consistent with prior research.^{4-6,11,13-16,19,41} As in other studies of breast carcinoma treatment in older

TABLE 4
Adjusted Odds of Systemic Therapy in Elderly Women with Localized Breast Carcinoma^a

Variable	Tamoxifen vs. no tamoxifen		Systemic chemotherapy vs. none		Adjuvant therapy consistent with 1995 St. Gallens Conference	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (yrs)						
67-79	1.00	—	1.00	—	1.00	—
80+	1.97	0.92-4.18	0.30	0.12-0.76	0.70	0.45-0.90
Stage						
I	1.00	—	1.00	—	1.00	—
IIA	2.69	1.62-4.46	3.92	2.05-7.47	3.10	1.83-5.23
IIB	2.74	0.85-8.84	8.11	2.32-28.35	6.50	1.59-26.53
Surgical treatment						
Breast conservation	1.08	0.56-2.10	11.25	4.61-27.44	2.29	1.29-4.05
Mastectomy	1.96	1.26-3.06	2.38	1.16-4.88	1.54	1.01-2.30
Breast conservation and radiation	1.00	—	1.00	—	1.00	—
Margin involved						
Yes	0.68	0.46-1.00	1.26	0.65-2.41	0.68	0.46-1.00
No	1.00	—	1.00	—	1.00	—
Referral to medical oncologist						
Yes	1.34	0.92-1.95	2.45	1.28-4.71	1.77	1.21-2.60
No	1.00	—	1.00	—	1.00	—
Axillary lymph node dissection						
Yes	1.00	—	1.00	—	1.00	—
No	0.75	0.49-1.16	1.40	0.62-3.14	0.79	0.51-1.22
Estrogen receptor						
Positive	4.30	2.23-8.28	0.24	0.10-0.58	6.31	3.19-12.45
Negative	1.00	—	1.00	—	1.00	—
Unknown	2.41	1.00-5.76	4.15	0.58-29.78	7.65	3.05-19.16
Progesterone receptor						
Positive	4.30	2.23-8.28	0.53	0.22-1.24	1.16	0.66-2.02
Negative	1.00	—	1.00	—	1.00	—
Unknown	2.41	1.00-5.76	0.06	0.01-0.38	0.66	0.31-1.39
Grade						
1	1.00	—	1.00	—	1.00	—
2	1.59	0.85-2.98	1.54	0.30-7.95	1.47	0.78-2.75
3	1.04	0.49-2.20	2.44	0.46-12.80	1.31	0.61-2.78
Unknown	1.30	0.74-2.29	1.80	0.38-8.39	1.33	0.76-2.33
No. of illnesses	1.06	0.94-1.19	1.11	0.90-1.36	1.08	0.96-1.21
Physical function ^b	1.00	0.99-1.00	1.03	1.01-1.04	1.01	1.00-1.01
Black	0.75	0.39-1.45	1.93	0.71-5.24	0.80	0.42-1.55
Education						
Lower than high school	1.00	—	1.00	—	1.00	—
High school or higher	0.87	0.61-1.25	1.14	0.61-2.13	0.90	0.62-1.29
HMO member	1.13	0.74-1.74	0.76	0.36-1.58	0.95	0.62-1.47
Private insurance	2.20	1.38-3.51	1.01	0.44-2.33	2.04	1.27-3.24
Cancer center	1.26	0.79-1.99	0.78	0.36-1.68	1.02	0.64-1.63
Region						
Massachusetts	1.00	—	1.00	—	1.00	—
Texas	0.46	0.27-0.79	0.81	0.32-2.07	0.40	0.23-0.70
Washington, DC	0.84	0.46-1.53	1.12	0.41-3.08	0.77	0.42-1.43
New York City	0.88	0.34-2.27	2.21	0.49-9.89	0.95	0.35-2.55
New York State	1.28	0.71-2.27	0.65	0.23-1.81	0.75	0.42-1.35
Year						
1997	1.00	—	1.00	—	1.00	—
1996	1.37	0.95-1.97	0.84	0.45-1.57	0.90	0.62-1.30
1995	0.96	0.51-1.81	1.00	0.35-2.82	0.74	0.38-1.38
C statistic	0.75	—	0.87	—	0.74	—

OR: odds ratio; CI: confidence interval; HMO: health maintenance organization.

^a Adjusted odds ratios, in which each variable is adjusted for the effects of all other variables in the table.

^b Odds for each 1-point increase on a scale from 0 to 100.

women,^{4,5,7,15,27,28,30,31,42} we noted that women in the Northeast (Massachusetts) were more likely to receive breast conservation and radiotherapy than women in other areas.

Patient preferences, including body image considerations, were also important independent predictors of local therapy patterns suggesting that elicitation of patient concerns and decision-making style^{43,44} should be a focus of patient-physician communication. Patient participation in decision making has additional implications beyond selection of therapy. In other research, women who feel that they have shared in the decision-making process are more likely to report being satisfied and have better posttreatment adjustment to cancer than women who feel that they did not participate.⁴⁵⁻⁴⁷ Because a substantial proportion of women in our study who did not receive radiotherapy and/or chemotherapy had been referred for radiation and medical oncology consultation, enhanced communication also may have a role in improving compliance with recommended treatment. Alternatively, unmeasured aspects of patient preferences and treatment-related inconvenience or travel⁴⁸ and/or scientific uncertainty may have contributed to this finding.

A very high proportion of women (87%) cited concern about cancer recurrence as important factor in their treatment decisions. However, in contrast to other research,⁴⁹ this was not an independent predictor of treatment in this older cohort. Possible explanations for this negative finding include limited response variability, the use of a single item to measure this domain, or a true null effect. Studies of breast carcinoma survivors also have yielded inconsistent results about the effects of treatment on women's fear of recurrence.⁵⁰⁻⁵² This is an important area for future investigation.

Another potentially important finding was that black women were twice as likely as white women to have radiotherapy omitted after breast conservation. Although not reaching the 0.05 level of significance, this was largely due to the small number of black women enrolled in the cohort (8%). Observations of differences in breast carcinoma treatment patterns by race have been noted in prior research.^{4,7,15,22} If confirmed in a larger sample of black patients with breast carcinoma, our results, and those of others, suggest that black women may have experiences with the health care system that differ from those of whites, which negatively impact on cancer treatment. This idea is supported by the findings from prior research that racial differences in treatment persist after control for sociodemographic factors.⁵³⁻⁵⁵ Others have suggested that race effects on cancer outcomes are

mediated by culturally based attitudes;⁵⁶ alternatively, blacks may experience discrimination in obtaining health care.

The major implication of our findings for local treatment, in which radiotherapy often is omitted after breast conservation among women 80 years and older, is that the risk of local recurrence may be increased.^{57,58} In postmenopausal women treated with breast conservation, the risk of local recurrence for Stage I or II disease without radiotherapy approaches 40% by 10 years.^{57,58} Because the life expectancy of the women in our study who received breast conservation alone was nearly 9 years, this pattern of care may place women at substantial risk for recurrences within their lifetimes.³⁸ Although local recurrence may not affect survival, it will impact a woman's quality of life.^{49,59} The use of radiotherapy among elderly breast carcinoma patients is currently the subject of clinical investigation and shifting clinical paradigms. For example, some studies have found that breast conservation followed by tamoxifen yields similar outcomes as breast conservation and radiotherapy.⁶⁰ Based on these observations, several national cooperative groups are conducting a randomized trial of the use of tamoxifen versus radiotherapy and tamoxifen after breast conservation among women 65 years and older.⁶¹ If equivalent, then omission of radiotherapy would not be considered undertreatment, if tamoxifen were used. Although women in our study who received breast conservation alone were the most likely to receive chemotherapy, they were not more likely to receive tamoxifen. Overall, it appears that many of the women 80 years and older were undertreated by current standards;⁵⁹ however, there remains substantial scientific uncertainty as to the most appropriate treatment for older women. This is a key area for future research.

There are several caveats that should be considered in evaluating our results, including the response rate and generalizability, study design, post hoc assessment, difficulty in controlling unobservable selection to surgeons, and power for race effects. Although the response rate observed in our cohort was 67.6%, this result is very similar to rates of participation observed in similar published studies.^{21,42} Nonparticipants were of a similar age as participants. Our cohort was drawn from a convenience sample of hospitals and includes a high proportion of patients cared for in cancer centers. As such, our results of the degree of nonstandard care is most likely to be an underestimate of trends in the general older population. Also, given known differences in regional variations^{5,9} and the lack of representation of all regions in our sample,

our results may not be representative of the entire U.S. elderly population. We currently are extending our research to confirm our results in a random sample of Medicare beneficiaries who have received a breast carcinoma diagnosis.

Our evaluation of determinants of treatment took place an average of 3 months after surgery. Although many demographic factors we assessed were not mutable, women's reports of factors considered in treatment decision making may be influenced by their actual selection of surgical approach. Unfortunately, prospectively observing the process of decision making involves a burden on women at a vulnerable time and was judged not feasible. Also, we asked women to recall their prebreast carcinoma functioning on average 3 months after their diagnosis and treatment. In other outcomes research, patient's retrospective report of their pre-event (e.g., myocardial infarction) functioning was fairly accurate.⁶² Although we considered physician's use of breast conservation in their practices, we cannot account for any unobservable selection of women to surgeons with particular treatment styles. Finally, we did not have a sufficient sample of black patients to make definitive statements about treatment in this group.

Despite these caveats, our results demonstrate that women 80 years and older are vulnerable to receiving less treatment than currently recommended in expert consensus guidelines.^{3,37} We cannot determine how much of this pattern is the result of patients' choice, failure to recommend treatment, lack of scientific evidence about the best treatment for older women, barriers to treatment, or other unmeasured determinates of treatment.

Older women, particularly those 80 years and older, are the fastest growing segment of the U.S. population² and will account for an increasing absolute number of breast carcinoma cases in the coming decades. Determination of the most appropriate regimens for this age group is an important research need. Additional research also is needed to confirm and extend our findings. Such efforts will be paramount to ensure that older women, including women 80 years and older, receive clinically appropriate treatment that maximizes their quality and quantity of life and is consistent with their preferences.

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Acculturation and Breast Cancer Screening Among Hispanic Women in New York City

ABSTRACT

Objectives. This study investigated whether acculturation was associated with the receipt of clinical breast examinations and mammograms among Colombian, Ecuadorian, Dominican, and Puerto Rican women aged 18 to 74 years in New York City in 1992.

Methods. A bilingual, targeted, random-digit-dialed telephone survey was conducted among 908 Hispanic women from a population-based quota sample. Outcome measures included ever and recent use of clinical breast examinations and mammograms. Multivariate logistic regression models were used to assess the effect of acculturation on screening use.

Results. When demographic, socioeconomic, and health system characteristics and cancer attitudes and beliefs were controlled for, women who were more acculturated had significantly higher odds of ever and recently receiving a clinical breast examination ($P \leq .01$) and of ever ($P \leq .01$) and recently ($P \leq .05$) receiving a mammogram than did less acculturated women. For all screening measures, there was a linear increase in the adjusted probability of being screened as a function of acculturation.

Conclusions. Neighborhood and health system interventions to increase screening among Hispanic women should target the less acculturated. (*Am J Public Health*. 1999;89:219–227)

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Despite the fact that Hispanic women have lower incidence rates for breast cancer than White non-Hispanic women, Hispanic women who do develop breast cancer are more likely to die of the disease.^{1–6} This mortality differential is, in part, related to Hispanics' being diagnosed at a later stage of breast cancer than White non-Hispanics, even after adjustment for socioeconomic status and duration of symptoms.^{2,7,8} This stage differential is likely related to differential screening use.^{6,9–11}

Socioeconomic status and having health insurance, having a usual source of care, and having a physician's recommendation for screening all predict screening use in both non-Hispanic and Hispanic women.^{11–16} Another factor that may influence breast cancer screening use by Hispanics is acculturation.^{17–22} Acculturation has been defined as "the psychosocial adaptation of persons from their culture of origin to a new or host cultural environment."^{23(p90)} For immigrants from non-English-speaking countries, acculturation includes the choice of language for use in daily life.²⁴

Previous studies of the role of acculturation in breast cancer screening have largely focused on Hispanics as a whole, and these studies have had mixed findings.^{17–21} When ethnic subgroups have been identified, the focus has been on Mexican Americans, and to a lesser extent on Cubans and Puerto Ricans, in California and the Southwest.^{17–21} The ethnic composition of New York City's Hispanic population (1 737 927 persons) differs from that of the southwestern United States; in 1990, the 4 largest Hispanic subgroups in New York City were Puerto Rican (49.5%), Dominican (19.1%), Colombian (5%), and Ecuadorian (4.5%).²⁵ The issue of acculturation and breast cancer screening among these northeastern Hispanics has received little attention. The purpose of this study was to assess the extent to which

acculturation plays a role in the use of recommended clinical breast examinations and mammograms in these 4 groups.

Methods

Survey Design and Sampling

This study was part of a larger study of cancer prevention and control needs of Caribbean-, Haitian-, and US-born Blacks and Puerto Rican, Dominican, Colombian, and Ecuadorian Hispanics living in New York City in 1992.^{15,26} The 4 Hispanic subgroups in the larger study comprised 908 women, who are the focus of this study. These 4 subgroups constituted the largest subgroups of Hispanics in New York City according to census data available at the time of the survey.^{25,27}

In the present study we used a quota sample to identify 50 women from each of 4 age groups—18 to 44 years, 45 to 54 years, 55 to 64 years, and 65 to 74 years—in each of 4 Hispanic groups, for an initial goal of 800 women. Because of an administrative oversight unrelated to sample characteristics, Dominicans aged 18 to 44 years were inadvertently oversampled. Since the quota sample was chosen to provide groups

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This paper was accepted June 18, 1998.

with similar age distributions, it allowed the acquisition of adequate numbers of respondents of all ages for each ethnic group.²⁸

A comparison of this quota sample's characteristics with those of an area probability sample, the sample of the Census Bureau's Current Population Survey during the same time period, suggests that our sample is comparable to the weighted probability sample of New York City Hispanics on several demographic parameters unrelated to the quota sampling framework.²⁹

The study sample was selected from the telephone exchanges for all 5 boroughs of New York City. Both list and random-digit-dialed sampling techniques were used to ensure coverage of households with unlisted numbers and members of the 4 ethnic groups. Targeting procedures employing census data, zip codes, and telephone exchanges were used to locate low-count ethnic groups clustering in specific neighborhoods.

Data Collection

Community leaders reflecting the cultural backgrounds of the study population were extensively involved in the study design and survey promotion. The instrument was developed with existing national survey items^{20,30-36} and modified for use in the target populations. New items were also designed and validated. The survey content areas were then reviewed by focus groups and community advisors from the ethnic communities. Spanish versions of the survey were pilot tested and were validated through standard translation and back-translation. Respondents could choose to be interviewed in Spanish or English. All data were collected via computer-assisted telephone interview from May to October 1992.

Dependent Variables

Use of clinical breast examinations and use of mammograms were the outcome measures. Two dichotomous variables were used for each screening procedure. The first variable was whether the respondent had ever had the procedure. She was asked, "Have you ever had a mammogram?" and "Have you ever had a breast physical exam by a doctor, nurse, or medical assistant?" The respondent was given definitions of the procedures before being asked about use.

The second dichotomous variable was whether the woman had recently been screened. She was asked, "When did you have your last mammogram?" and "About how long has it been since you had a breast physical exam by a doctor, nurse, or medical assistant [≤ 1 , 1-2, 2-3, or >3 years]?"

TABLE 1—Characteristics of the Sample of Hispanic Women (n = 908) in a Study of Cancer Prevention and Control Needs: New York City, 1992

	Ethnicity, %				P
	Colombian (n = 202)	Dominican (n = 308)	Ecuadorian (n = 151)	Puerto Rican (n = 247)	
Age, y					
18-44	31.2	50.7	34.4	37.3	
45-54	24.7	16.6	32.5	20.7	
55-64	25.3	16.6	22.5	21.1	
≥ 65	18.8	16.2	10.6	21.1	.001
Education					
<12 y	40.6	51.6	45.7	46.1	
12-15 y	45.5	37.6	46.4	40.9	
College graduate	13.9	10.7	7.9	13.0	.161
Marital status					
Married	45.5	41.2	53.0	36.4	
Single	54.5	58.7	45.7	62.7	.008
Household income, \$					
<20 000	38.6	49.0	37.1	35.2	
$\geq 20 000$	26.2	22.4	25.2	38.1	
Missing ^a	35.1	28.6	37.6	26.7	.001
Health status					
Excellent-very good	32.7	33.1	37.1	32.8	
Good	33.2	23.4	28.5	32.0	
Fair-poor	30.2	39.6	33.8	31.6	.321
Age at immigration, y					
≤ 16	9.4	18.2	7.3	53.9	
> 16	90.6	81.8	92.7	46.1	.001
Interview language					
English	9.4	14.0	8.6	42.1	
Spanish	90.6	86.0	91.4	57.9	.001
Acculturation					
Lower	75.7	76.9	77.5	37.8	
Higher	24.3	23.1	22.5	62.2	.001
Employment status					
Unpaid	43.1	52.6	36.4	39.3	
Retired	12.9	15.3	15.9	17.8	
Part-time	14.4	5.2	7.3	6.9	
Full-time	29.2	26.3	39.1	35.2	.001
Insurance status					
Uninsured	35.6	26.0	36.4	8.1	
Medicaid/Medicare only	22.8	43.2	27.8	40.5	
Private	39.1	28.6	33.1	49.0	.001
Has a usual source of care	80.7	80.5	82.8	90.7	.006

^aIncome was missing for women who refused to answer the question or answered "Don't know."

"Recent" was defined according to 1992 American Cancer Society (ACS) guidelines for routine screening³⁷: for clinical breast examination, every year for women older than 40 years and every 3 years or less for women aged 20 to 40 years, and for mammogram, every 2 years or less for women aged 45 years and older. Women aged 40 to 44 years were excluded from mammogram analyses because of the quota sample structure. An age-related screening "rigor" variable was also included, reflecting the fact that the quota ages included groups of women for whom recommended screening intervals differed.

Independent Variables

Since language is an important component of modifiable aspects of the process^{38,39} of breast cancer screening, we chose to focus on linguistic aspects of acculturation. Other indicators of acculturation (recency of immigration, proportion of life spent in mainland US, age at immigration, whether respondent was first or second generation, and language of interview) were available; however, these were not included in our acculturation scale or multivariate models because they were highly correlated and displayed strong multicollinearity with the acculturation scale.⁴⁰

TABLE 2—Selected Characteristics (%) of the Sample of Hispanic Women (n = 907^a), by Acculturation Level: New York City, 1992

	Acculturation		P
	Lower (n = 307)	Higher (n = 600)	
Age, y			
18–44 (n = 362)	32.0	55.4	
45–54 (n = 201)	23.2	20.2	
55–64 (n = 188)	23.5	15.3	
≥65 (n = 156)	21.3	9.1	.001
Education, y			
<12 (n = 424)	58.8	23.1	
12–15 (n = 379)	33.2	58.6	
≥16 (n = 104)	8.0	18.3	.001
Household income, \$			
<20 000	46.7	30.0	
≥20 000	16.0	51.1	
Missing ^b	37.3	18.9	.001
Usual site of care			
Private doctor's office	39.4	45.4	
Hospital outpatient department	15.6	14.8	
Public health clinic	8.1	6.3	
HMO	10.8	8.6	
Emergency room	8.9	9.5	
No usual site	17.1	15.4	.525
Insurance status			
Private insurance (n = 337)	25.3	60.3	
Only Medicare or Medicaid (n = 321)	41.7	23.1	
Uninsured (n = 227)	30.2	15.0	.001
Proportion of life spent in mainland US, %			
<25 (n = 343)	37.5	9.9	
26–50 (n = 317)	43.2	20.2	
51–75 (n = 181)	16.4	27.8	
>75 (n = 53)	2.8	42.1	.001
Age at immigration, y			
≤16 (n = 218)	8.3	54.7	
>16 (n = 689)	91.7	45.3	.001

^aIn some categories, n's may not add up to 907 because some women refused to answer the question or answered "Don't know." There were no significant differences between the numbers of women with higher and lower acculturation scores in the "don't know/refused" category for any variable except income.

^bIncome was missing for women who refused to answer the question or answered "Don't know."

Our acculturation measure was a continuous variable based on a 12-item scale (available from the authors). These items were drawn from a 26-item acculturation scale developed by Burnam et al.²³ and later validated in the shortened form in a New York City Hispanic population by Epstein et al.²⁴ This scale was reliable in our sample (Cronbach $\alpha = .93$). The 12 items asked about language and media (television, radio, books, magazines, newspapers) use in a variety of situations (work, home, neighborhood, shopping) and with different people (including spouses or partners, children, parents, and friends). For each item, the 5 response options were as follows: 1 = only Spanish, 2 = mostly Spanish, 3 = Spanish and English, 4 = mostly English, and 5 = only English. Acculturation level was calculated as a mean score of these 12 items (1 = least accultur-

ated, 5 = most acculturated).²³ (For ease of understanding, in Tables 1–3 the acculturation score is dichotomized into "lower" [score ≤ 2.5] and "higher" [score > 2.5]. In Table 4 [multivariate models], the acculturation score is continuous.)

Controlling variables included socio-demographics (age, education, marital status, income, employment); health status (self-assessed 5-item measure, ranging from "poor" to "excellent"); site of care; presence of a usual source of care; insurance status (uninsured, public insurance only [i.e., Medicare or Medicaid], or private insurance); and cancer attitudes and beliefs.^{8,11,41–48} Since approximately 30% of the respondents refused to provide data on income, this variable was included in the multivariate analyses by keeping the refusals as a separate dummy variable.

Cancer attitudes were measured with the Cancer Attitudes Scale.^{26,49} This scale includes an anxiety subscale (6 items, Kuder-Richardson-20 = 0.57) and a hopelessness subscale (8 items, Kuder-Richardson-20 = 0.65). Perceived risk for developing cancer was measured with 2 items ($r = 0.70$) and concern about cancer was measured with 2 items ($r = 0.72$).²⁶

Analysis

Bivariate analyses were performed to assess relationships among categorical variables. Statistical significance in cross-tabulations was evaluated with the χ^2 statistic. We tested for interactions between acculturation (dichotomized) and several potential effect modifiers with respect to screening use: education, insurance status, income, and health status.⁴⁷ For women who chose to do the interview in Spanish, an additional test for interaction between acculturation and language of the health care provider was performed. No significant interactions were found between acculturation and income, insurance status, or health status in predicting screening use. There was a tendency for education to modify acculturation's effect on screening; however, estimates for these interaction terms were highly unstable in the multivariate logistic regressions and were not included in the final models.

Stepwise logistic regression models assessed the effect of acculturation and controlling variables on each of the cancer screening outcomes. Variables that had at least 1 significant dummy (α level for stepwise regression = .20) were included in the final model. All models exhibited goodness of fit by the Hosmer-Lemeshow test.⁵⁰

The parameter estimates from the final multivariate logistic regression models were then entered into the logit function to calculate the adjusted probabilities of screening for each of the 5 levels of acculturation.⁵¹ An additional model was created for the subgroup of women who completed the interview in Spanish (n = 726). This model was the same as the overall final logistic regression model for the entire group (n = 907), with the addition (one at a time) of variables on language and its importance in the health care setting (whether the physician spoke Spanish, importance of physician's speaking Spanish, importance of someone in the clinic's speaking Spanish). All analyses were performed with SAS.⁵²

Results

A total of 908 Hispanic women completed the survey. The overall response rate

TABLE 3—Percentage (Unadjusted) of Hispanic Women Receiving Breast Cancer Screening, by Selected Characteristics: New York City, 1992

	Clinical Breast Examination		Mammography	
	Ever (n = 888)	Recent ^a (n = 882)	Ever (n = 542)	Recent ^a (n = 524)
Total sample	86.3	68.1	71.6	62.0
Demographic characteristics				
Age, y				
18–44	85.3	77.8
45–54	85.1	59.2	66.7	58.5
55–64	90.9	68.5	74.7	66.5
≥65	84.5	58.1**	74.2	61.2
Ethnicity				
Colombian	87.9	66.3	73.4	62.7
Dominican	80.5	64.7	66.9	53.4
Ecuadorian	85.3	69.6	68.4	62.5
Puerto Rican	92.6**	72.9	76.6	69.9*
Marital status				
Married	86.1	70.0	68.2	61.3
Single, divorced, widowed	86.5	66.7	73.6	62.2*
Socioeconomic characteristics				
Education				
<12 y	83.2	59.2	69.3	59.3
12–15 y	88.0	74.4	73.7	66.3
College graduate	92.4*	81.7**	78.0	65.8
Household income, \$				
<20 000	83.9	63.9	68.6	60.2
≥20 000	92.0	81.8	78.4	77.6
Missing ^c	84.2**	61.3**	71.1	55.7**
Employment status				
Unpaid	87.8	65.4	69.3	59.2
Retired	84.1	61.2	75.5	61.9
Part-time	87.5	70.4	67.4	61.9
Full-time	88.6	74.8*	72.5	66.4
Insurance status				
Uninsured	77.5	53.4	53.4	45.4
Medicaid/Medicare only	88.2	68.0	77.5	63.7
Private	91.0**	78.3**	76.3	70.3**

(Continued)

was 62.3% (includes all calls made to identify homes of persons of the ethnic and age groups of interest). Among women who qualified on the basis of age and ethnicity, the rate of refusal to complete the survey was 2.1%.

Table 1 presents the characteristics of the specific Hispanic subgroups. Dominicans tended to be younger and to have lower incomes than members of the other groups. A higher percentage of Puerto Ricans than of the others came to the mainland United States by age 16 years. Puerto Ricans were also more likely than the others to use English for the interview and to have some form of health insurance.

Table 2 presents selected characteristics of women with lower and higher acculturation scores. These characteristics were highly correlated with acculturation (proportion of life spent in the United States, age at immigration) or were significant predictors of screening use in the final multivariate mod-

els (age, education, insurance status, income, type of site of care/usual source of care).

Having higher acculturation, having a usual source of care, having higher income, having health insurance, immigrating to the United States before the age of 16 years, spending a greater proportion of one's life in the United States, and use of English for the interview were each statistically significantly associated in univariate analyses with greater receipt of ever and recent clinical breast examination and mammography (Table 3).

The final multivariate logistic regression models (Table 4) showed that when other covariates were controlled for, women who were more highly acculturated were significantly more likely than less acculturated women to have obtained a clinical breast examination, both ever and recently ($P \leq .01$), and to have ever ($P \leq .01$) and recently ($P \leq .05$) received a mammogram.

The mean adjusted probabilities of screening as a function of acculturation are shown in Figure 1. For all tests, there is a linear increase in the adjusted probability of screening as one goes from least to most acculturated.

Of the 908 women interviewed, 726 chose to be interviewed in Spanish. These women were asked whether the doctor at their usual site of care spoke Spanish and about the importance of either their doctor's or other clinical personnel's speaking Spanish. Although 89% of the women with lower acculturation scores felt it was important that their doctor speak Spanish, only 49% of those with higher acculturation scores felt this was important ($P = .001$). Similar proportions of more and less acculturated women felt it was important that someone in the clinic speak Spanish (89% vs 51%, respectively; $P < .001$). Surprisingly, in this subset of 726 women, having a primary care doctor who spoke Spanish was not significantly associated with higher odds of receipt of ever or recent clinical breast examinations or mammograms (data not shown).

Discussion

Previous studies on breast cancer screening and acculturation have focused on Mexican Americans in California and the Southwest; this study is unique in its focus on Colombian, Dominican, Puerto Rican, and Ecuadorian Hispanic women in New York City. For these women, greater acculturation was significantly associated with higher rates of screening by clinical breast examination and mammogram. This relationship held after adjustment for socioeconomic status, health status, demographic and health system characteristics, and cancer attitudes and beliefs. Consistent with the findings of previous studies, having insurance remained a major predictor of screening use.¹⁶

Previous studies on breast cancer screening and acculturation have had conflicting results. Some found no statistically significant effect of acculturation on screening utilization,^{17–19,22,53} while others did find an effect.^{20–21} The studies that found no significant effect all^{17–19,22} used a broad measure of acculturation that included not only language use but also social patterns, family values, or ethnic identification. One of the studies that found a significant association between acculturation and screening used a measure that included language, ethnic identification, and birthplace,²⁰ and the other used only language chosen for the interview.²¹

Placing our results in the context of these previous conflicting findings is compli-

TABLE 3—Continued

	Clinical Breast Examination		Mammography	
	Ever (n = 888)	Recent ^a (n = 882)	Ever (n = 542)	Recent ^a (n = 524)
Health/health system characteristics				
Health status				
Excellent—very good	87.8	70.5	69.4	62.9
Good	86.9	70.8	74.8	66.7
Fair—poor	83.3	62.0*	71.0	58.6
Usual source of care				
Yes	88.7	71.5	75.4	65.8
No	73.6**	50.7**	48.7**	39.5**
Usual site of care				
Private doctor's office	89.5	69.8	71.7	62.9
Emergency room	87.7	72.8	71.1	59.1
Hospital outpatient department	89.6	75.0	88.6	80.5
Public health clinic	87.9	69.7	77.8	62.8
HMO/large health center	88.8	75.0	80.0*	69.5*
Acculturation				
Language preferred for interview				
English	95.8	86.1	81.0	75.9
Spanish	84.0**	64.0**	70.4	60.4*
Age at immigration, y				
≤16	93.1	80.5	83.3	74.3
>16	84.3**	64.5**	69.8*	60.1*
Proportion of life spent in mainland US, %				
≤25	76.4	59.0	60.0	51.9
26–50	87.5	69.1	72.7	61.9
51–75	90.6	67.4	76.3	67.7
>75	98.1	84.6	87.1	80.6
Born in mainland US	95.0**	87.3**	81.2**	71.4*
Acculturation ^d				
Higher	94.5	80.8	79.4	73.4
Lower	82.2**	62.0**	68.9*	58.3**
Cancer attitudes and beliefs				
Cancer anxiety scale				
High	84.6	66.0	70.6	61.1
Low	88.4	70.8	73.1	63.6
Cancer hopelessness scale				
High	84.3	64.3	70.1	69.2
Low	91.8**	78.9**	76.9	57.7**
Concern about cancer				
High	87.5	72.9	71.9	64.8
Low	85.3	64.4**	71.4	60.0
Perceived risk of cancer				
High	86.3	70.3	71.4	62.2
Low	86.2	65.7	71.8	61.9

^a"Recent" was defined according to 1992 American Cancer Society guidelines, as follows: for clinical breast examination, every year for women older than 40 years and every 3 years or less for women aged 20 through 40 years; for mammography, every 2 years or less for women aged 45 years and older. (Hence, total n's do not add up to 908.)

^bNot applicable.

^cIncome was missing for women who refused to answer the question or answered "Don't know."

^dMean acculturation scores (see text) were as follows: for clinical breast examination, ever vs never = 2.2 vs 1.7*, recent vs not recent = 2.3 vs 1.8*; for mammography, ever vs never = 2.0 vs 1.7*, recent vs not recent = 2.1 vs 1.8*.

* $P \leq .05$ for the group (cell); ** $P \leq .01$ for the group (cell).

cated by the controversy over deciding how best to measure acculturation and determining the conceptual framework within which acculturation operates. With respect to the first area, some criticize the use of language preference alone as an inadequate measure of acculturation; they contend that the extent to

which a person has adopted core values of the host culture should be included.⁵⁴ Others argue that language preference is the best measure of cultural integration.^{55–57} Many now view language as a reliable shorthand measure of acculturation, because it accounts for the greatest portion of variance of accul-

turation scales and because it is valid.^{58,59} We chose to focus on the linguistic aspects of acculturation because of their relevance to interventions targeting the delivery of health care.

Measures of acculturation that focus on language use have another advantage over broader measures of acculturation: one can establish that language use is associated with the screening behavior. With mixed acculturation measures, components unrelated to the behavior of interest could lower the association between language use and health behavior, perhaps explaining the inconsistency of previous findings in studies of acculturation and health practices of Hispanic adults.^{23,24,60}

The second area of controversy is the conceptual framework within which acculturation operates. Limited proficiency in English is associated with socioeconomic factors known to be related to decreased use of health care services.^{21,61} If these factors are not controlled for, acculturation may simply act as a proxy for socioeconomic status.⁵⁴ Our inclusion of socioeconomic indicators (income, education, work status) in the multivariate models reduces this risk.

Also complicating the conceptual framework is the issue of how language influences health care use. Some see language as a communication barrier between health care provider and patient,⁶² while others emphasize the effect on screening practices of language as an access factor.²⁰ Viewing language acquisition as merely an "access factor" may be an oversimplification. Language influences perceptions, cognitive structure, and self-expression,^{63–66} which may affect how Hispanic women interact with providers. Thus, it is likely that language operates on both levels and that some combination of its effects contributes to the likelihood that a woman will obtain recommended screening.

As an example of language's complex role, we found that among the subset of women who chose to be interviewed in Spanish and who were the least acculturated, having someone in the clinic who spoke Spanish was not predictive of screening use. One implication of this finding is that simply introducing translators or Spanish speakers into the clinic, without addressing patients' level of acculturation, may not be sufficient to change behavior. It might be necessary, for example, to involve trained lay health workers from cultural backgrounds similar to those of the target population.⁶⁷

Further community- and practice-based research is needed to evaluate the effectiveness of tailoring cancer screening messages to the acculturation level of the women being served. Further study would also help to clar-

TABLE 4—Acculturation and Adjusted Odds^a of Breast Cancer Screening in a Sample of Hispanic Women: New York City, 1992

	Odds Ratio (95% Confidence Interval)			
	Clinical Breast Examination		Mammography	
	Ever	Recent ^b	Ever	Recent ^b
Acculturation ^c	1.82** (1.30, 2.60)	1.35** (1.07, 1.71)	1.59** (1.17, 2.17)	1.34* (1.01, 1.79)
Usual site of care				
Private doctor's office	1.25 (0.60, 2.49)	0.84 (0.48, 1.44)	1.11 (0.54, 2.21)	1.13 (0.57, 2.21)
Hospital outpatient department	1.53 (0.66, 3.54)	1.24 (0.65, 2.35)	4.00** (1.58, 10.7)	3.40** (1.48, 8.02)
Public health clinic	1.55 (0.59, 4.28)	0.97 (0.47, 2.04)	1.82 (0.66, 5.28)	1.33 (0.52, 3.47)
HMO	1.47 (0.59, 3.79)	1.30 (0.64, 2.66)	2.02 (0.82, 5.15)	1.69 (0.73, 3.99)
Emergency room	1	1	1	1
No usual site	0.56 (0.27, 1.13)	0.43** (0.23, 0.77)	0.56 (0.25, 1.21)	0.56 (0.26, 1.22)
Education, y				
<12	1	1	1	1
12–15	1.24 (0.76, 2.04)	1.39 (0.96, 2.02)	1.12 (0.69, 1.83)	1.11 (0.70, 1.79)
≥16	1.86 (0.82, 4.71)	1.90* (1.05, 3.59)	1.25 (0.55, 3.10)	0.89 (0.41, 1.98)
Age, y				
20–44	1	1	NA	NA
45–54	1.48 (0.85, 2.62)	0.68 (0.33, 1.32)	1	1
55–64	3.20** (1.66, 6.35)	1.25 (0.61, 2.49)	1.71* (1.06, 2.80)	1.45 (0.81, 2.59)
≥65	1.16 (0.60, 2.25)	0.66 (0.31, 1.34)	1.17 (0.66, 2.07)	1.03 (0.54, 1.95)
Insurance				
Private	1.62 (0.92, 2.86)	2.10** (1.36, 3.24)	1.75* (1.00, 3.07)	1.49 (0.87, 2.57)
Public only	2.55** (1.47, 4.49)	2.26** (1.47, 3.51)	2.47** (1.38, 4.47)	1.74* (1.01, 3.03)
Uninsured	1	1	1	1
Income, \$				
<20 000	0.78 (0.41, 1.45)	0.70 (0.43, 1.10)	0.77 (0.40, 1.47)	0.56 (0.30, 1.04)
≥20 000	1	1	1	1
Missing ^d	0.90 (0.44, 1.82)	0.79 (0.47, 1.32)	1.01 (0.51, 2.00)	0.49* (0.25, 0.94)

Note. Only statistically significant variables from the final model are shown. 1 = reference category; NA = not applicable.

^aAll odds ratios are adjusted for acculturation, type of site of care/usual source of care, education, age, ethnicity, insurance status, marital status, health status, cancer anxiety score, cancer hopelessness score, cancer concern score, and income.

^b"Recent" was defined according to 1992 American Cancer Society guidelines as follows: for clinical breast examination, every year for women older than 40 years and every 3 years or less for women aged 20 through 40 years; for mammography, every 2 years or less for women aged 45 and older (40–44-year-olds excluded because of quota sample structure).

^cAcculturation is continuously scaled from 1 (least acculturated) to 5 (most acculturated). Odds ratios for this variable indicate increase in odds of screening per unit increase in the acculturation scale.

* $P \leq .05$; ** $P \leq .01$.

ify whether having health care providers with a common language or cultural orientation could lead to improved screening rates for Hispanic women.

Several factors should be considered in interpreting our data, including potential selection bias, use of self-report, and a potential lack of generalizability to persons without telephones or living in rural areas. The women who participated in this study may differ systematically from the nonparticipants; for example, participants may be more likely to have had screening. We do not have data on the nonparticipants. However, the refusal rate among those known to be eligible for the study was low (2.1%).

Use of screening services in this study was determined by self-report. Since the women received care from a variety of settings in New York City, validation of self-reports through medical record review was not practical. Several studies have established that self-reporting usually overestimates the preva-

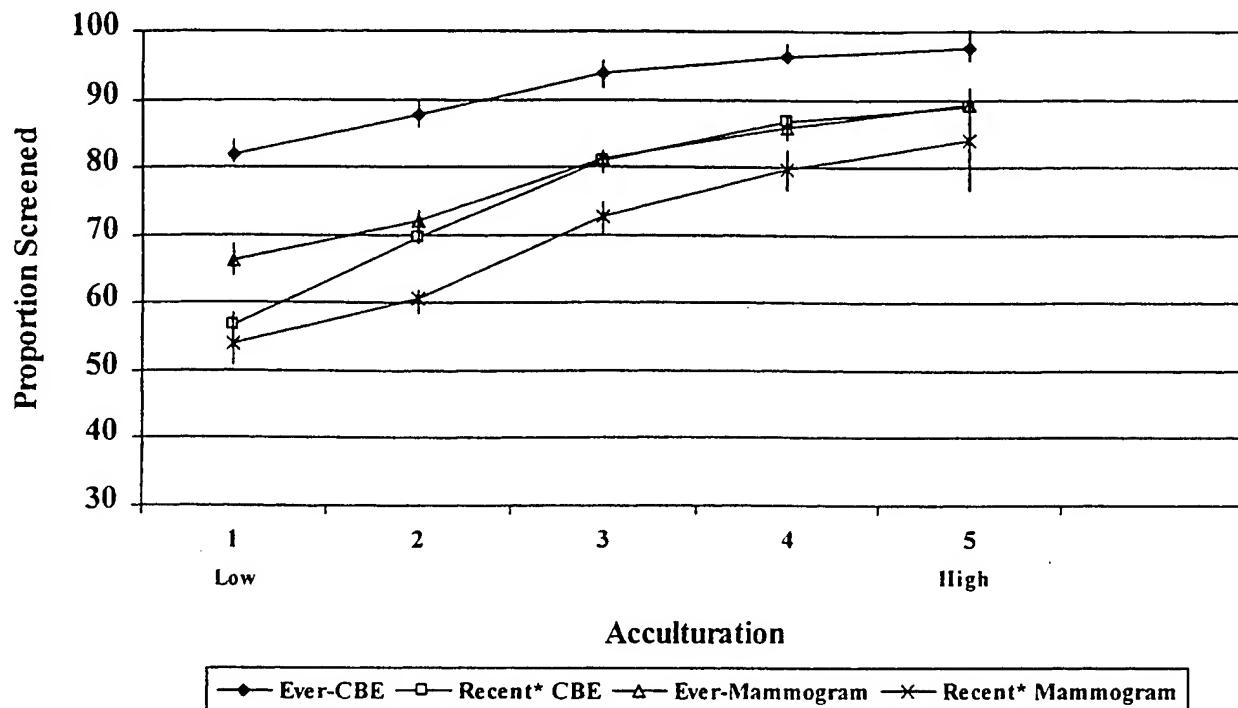
lence of screening.^{66–71} Characteristics that might influence the validity of self-reports, such as acculturation, education and socioeconomic status, have been controlled for in analyses assessing the sample as a whole.

The rates of receipt of clinical breast examination and mammography in our 1992 study seem high relative to commonly cited national rates, most of which are based on data from 1987 and earlier. However, our screening rates are consistent with those from more recent local studies³⁵ and with Behavioral Risk Factor Surveillance System data from the same period. For instance, a Centers for Disease Control and Prevention study of these data for 39 states⁷² found that age-adjusted proportions of women aged 40 years and older who received a mammogram in the preceding 2 years ranged from 43.8% to 65.2% in 1989 and from 63% to 79.7% in 1995.

While the vast majority of Hispanic residents of New York State resided in New York City at the time of the survey,²⁷ our data may

not be generalizable to Hispanic women living in, or migrating to, rural settings. In 1992, 79% of Hispanic households in New York City had telephones.⁷³ Personal interviews, the alternative to telephone interviews, are difficult to achieve in the economically depressed areas of New York City where many of the target populations live, because of residents' concern for security. Furthermore, in-person screening for quota samples is extremely inefficient. Despite this limitation, the quota sample is broadly representative of the ethnic groups living in the targeted areas.

An upward trend in screening use among Hispanic women, compared with older data, is reflected in our results and those of other recent studies.^{16,68,74} However, recent mammography use is still reported by a higher proportion of Anglo Americans (79%)¹⁶ than either Mexican Americans (61%)¹⁶ or our sample of Hispanic women (52%). Nationally, the same is true of recent clinical breast examination (66% [Anglos] vs 59% [Hispan-



Notes. Vertical line indicates the 95% confidence interval for that adjusted proportion.

"Recent" was defined according to 1992 American Cancer Society guidelines as follows: for clinical breast examination, every year for women older than 40 years and every 3 years or less for women aged 20 through 40 years; for mammogram, every 2 years or less for women aged 45 and older.

Adjusted proportions of women screened are calculated from the logit function based on the multivariate logistic regression models (see Table 3), which adjust for acculturation; type of site/usual site of care; education; age; ethnicity; insurance status; marital status; health status; cancer anxiety, hopelessness, and concern scales; and income.

FIGURE 1—Adjusted proportions (with 95% confidence intervals) of Hispanic women receiving breast cancer screening, level of acculturation.

ics)).⁷⁴ In our sample, recent clinical breast examination rates were slightly higher (68%), especially among the more acculturated.

The Department of Health and Human Services already recognizes the importance of language and culture in health promotion programs serving minority populations and has established a year 2000 goal to "increase to at least 50% the proportion of counties that have established culturally and linguistically appropriate community health promotion programs for racial and ethnic minority populations."⁹ Our finding of a strong association between a woman's level of acculturation and whether or not she receives recommended screening reinforces the importance of acculturation in the delivery of breast cancer screening programs to women in these Hispanic subgroups. Although the more acculturated women in this study had screening rates near or even exceeding those set as year 2000 goals—defined as 80% of Hispanic women aged 40 and over have ever received and 60% of Hispanic women aged 50 and over have recently received clinical

breast examination and mammography—less acculturated women still have a long way to go if they are to achieve those objectives. The fact that recency of immigration was associated with screening and was strongly collinear with acculturation suggests that targeting programs to areas with a high proportion of recent immigrants may be a useful way to reach less acculturated Hispanic women. □

Contributors

Ann O'Malley developed the research question, performed all data analyses, and wrote the manuscript for this paper. Jon Kerner and Jeanne Mandelblatt were both principal investigators on the National Cancer Institute study responsible for the collection of the dataset and contributed to writing the manuscript. Ayah Johnson provided statistical guidance for the project.

Acknowledgments

This research was supported by grant DAMD 17-97-1-7131 from the US Department of the Army (Dr O'Malley, principal investigator) and grant R01

CA53083 from the National Cancer Institute (Dr Kerner, principal investigator).

We thank Barbara Muth, Patrick G. O'Malley, MD, MPH, and the reviewers for their helpful comments on this manuscript.

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CORE 2

APPENDIX 2.

Quality of Life Library

References and Sample Instrument Abstraction Forms

Quality of Life

Title	Authors	Date
Cost Effectiveness in Health and Medicine	Marthe R. Gold, Joanna E. Siegel, Louise B. Russell, Milton C. Weinstein	1996
Health Care Cost Management: A Basic Guide Third Edition	Madelon Lubin Finkel	1996
Understanding and Choosing Clinical Performance Measures for Quality Improvement: Development of a Typology	Benjamin Duggar, James DeLozier, David Goldenberg, R. Heather Palmer, Ann G. Lawthers, Naomi J. Banks, David Kurland J. Lee Hargraves, Laura Peterson	January 31, 1995
Outcomes Management and Resources Allocation: How Should Quality of Life Be Measured?	D.C. Hadorn	July, 1993
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Tools for Evaluating Health Technologies: Five Background Papers	Floyd J. Fowler, Jeff Whittle, Julie E. Buring, Micheal A. Jonas, Charles H. Hennekens, Matthew P. Longnecker, Neil R. Powe, Robert I. Griffiths	February 1995
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Methods of Cost Effectiveness Analysis: Areas of Consensus and Debate	Byran R. Luce, Ph.D., Kit Simpson, Dr. P.H.	April 22, 1993
A Practical Guide to Prevention Effectiveness: Decision and Economic Analyses	Prevention Effectiveness Activity Epidemiology Program Office Centers for Disease Control and Prevention	
Improving Survey Questions : Design and Evaluation Applied Social Research Methods Series Volume 38	Floyd J. Fowler, Jr.	1995
Reliability and Validity Assessment	Edward G. Carmines and Richard A Zeller	1979
Decisions with Multiple Objectives: Preference and Value Tradeoffs	Ralph L. Keeney and Howard Raiffa	1993
Health Outcomes for Older People : Questions for the Coming Decade	Institute of Medicine	1996

Title	Authors	Date
Health Economics	Charles E. Phelps	1992
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Breast Cancer Chemotherapy Questionnaire

Measure: BCCQ or BCQ

Contact Person: Mark N. Levine, M.D.
Hamilton Regional Cancer Center
699 Concession Street
Hamilton, Ontario L8V 5C2
Canada
Phone: (416) 387-9495

Terms of Use: N/A. Contact the above.

General or Disease Specific: Breast cancer specific- stage II

Number of Items: 32

Domain: There is only one overall score but 7 domains have been identified

- consequences of hair loss
- emotional dysfunction
- physical symptoms
- trouble and inconvenience associated with treatment
- fatigue
- nausea
- positive well being

Administration Time: 10-15 minutes

Mode of Administration: Interview administered

Time Frame: "During the last four weeks"

Scoring: Each question has a 7 point Likert scale. The final score is the mean of the 32 questions with lower scores indicating a higher QoL.

Preference Based: No.

Population Used In: N/A

Reliability and Validity:

Validity:

correlation coefficients: between BCQ and

Karnofsky	r=.46
Rand Physical	r=.60
Rand Emotional	r=.58
Spitzer	r=.62
Global (patient physical and emotional)	r=.41-.51

Reproducibility:

-Mean change scores in stable patients for the BCQ was -0.183 while other tests ranged from 0.041 (Karnofsky) to -0.560 (Spitzer).

Comments:

N/A

References:

Levine MN, Guyatt GH, Gent M, et al. Quality of Life in Stage II Breast Cancer: An Instrument for Clinical Trials. *Journal of Clinical Oncology* 1988; 6(12): 1798-1810.

Brief Symptom Inventory

Measure: BSI

Contact Person: National Computer Systems, Inc.

1-800-627-7271 ext. 5151

Fax: 612-939-5199

email: assessment@ncs.com

Terms of Use: The instrument is copyrighted and a fee is required for the manual. For copies of the instrument, the price of scoring is included. Variable cost depending on number of instruments. No royalty fee required.

General or Disease Specific: General Psychological

Number of Items: 53

Domain:

General Indices:

- Global Severity Index (GSI)
- Positive Symptom Distress Index (PSDI)
- Positive Symptom Total (PST)

Primary Symptom Dimensions:

- Somatization (SOM)
- Obsessive-Compulsive (OC)
- Interpersonal Sensitivity (I-S)
- Depression (DEP)
- Anxiety (ANX)
- Hostility (HOS)
- Phobic Anxiety (PHOB)
- Paranoid Ideation (PAR)
- Psychotism (PSY)

Administration Time: 8-10 minutes

Mode of Administration: Self-Administration

Time Frame: "during the past week, including today."

Scoring: Each item is based on a 0-4 scale with 0 being "not at all" bothered and 4 representing "extremely" bothered. Ratings on the items that make up a given scale are summed and then divided by the number of items rated. Higher scores indicate higher distress.

Preference Based: No

Population Used In:

- in Hodgkin's Disease Survivors¹
- in a rural community²
- in an elderly population³⁴
- for psychosocial screening of cancer patients⁵

- in patients and husbands adjusting to breast cancer⁶
- in patients who completed and dropped out of chemotherapy⁷
- in adult and adolescent patients⁸
- in adult psychiatric patients⁹
- in patients with lung cancer¹⁰
- in a controlled clinical trial for the reduction of pain and nausea during cancer treatment¹¹
- in gynecological and breast cancer patients adjusting to the cancer diagnosis (comparisons with males and females having other cancer sites)¹²
- in adolescents with cancer¹³
- in a cancer pain study¹⁴
- among the spouses of terminally ill cancer patients¹⁵
- families coping with pediatric leukemia, ten years after treatment¹⁶
- in patients with advanced breast cancer treated with chemotherapy¹⁷
- in women and their husbands adjusting to recurrent breast cancer¹⁸
- in Asian, Asian-American, and European- American college students¹⁹
- in adult leukemia survivor²⁰
- in ethnically diverse female patients²¹
- in different lengths of stay at hospices for cancer patients²²
- in women with suspected breast cancer²³
- in women with a family history of breast cancer²⁴
- in advanced stage Hodgkin's disease patients and acute leukemia survivors²⁵

Reliability and Validity:

- internal consistency: Cronbach's alphas ranged from .71 (PSY) to .85 (DEP).
- test-retest reliability: range of .68 (SOM) to .91 (PHOB)

Note: -an information packet is being sent with necessary information pertaining to reliability and validity.

Comments:

- appropriate for ages 13 and older
- written at a 6th grade reading level
- more information can be found at: <http://assessments.ncs.com/assessments/tests/bsi.htm>

References:

Piersma HL, Reaume WM, Boes JL. The Brief Symptom Inventory (BSI) as an outcome measure for adult psychiatric inpatients. *Journal of Clinical Psychology* 1994; 50(4):555-563.

¹ **Kornblith AB, Anderson J, Cella DF, et al.** Quality of life assessment of Hodgkin's disease survivors: a model for cooperative clinical trials. *Oncology (Huntingt)* 1990 May;4(5):93-101; discussion 104.

² **Carscaddon DM.** Predicting psychiatric symptoms in rural community mental health clients. *Psychol Rep* 1990 Apr;66(2):561-2.

³ **Harper RG, Kotik-Harper D, Kirby H.** Psychometric assessment of depression in an elderly general medical population. Over- or underassessment? *J Nerv Ment Dis* 1990 Feb;178(2):113-9.

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Cancer Rehabilitation Evaluation System

Measure: CARES

Contact Info: C. Anne Coscarelli Schag
CARES Consultants
2210 Wilshire Blvd, Suite 359
Santa Monica, California 90403
USA:

Phone Number: (213) 450-7410

Terms of Use: Permission is needed and fees are required.

Disease Specific or General: Cancer General

Number of Questions: There are 139 total items of which 88 are completed by all patients. The remaining items (divided into 10 subscales) are completed if the specific subscales apply to the patient.

Domain:

- Overall Scale Score
- 5 summary scales
- 31 subscales
 - Physical
 - ambulation
 - recreational activities
 - activities of daily living
 - difficulty working
 - pain
 - weight loss
 - clothing
 - Psychosocial
 - difficulty communicating with friends/relatives
 - anxiety in medical situations
 - psychological distress
 - worry
 - friends/relatives difficulty interacting
 - cognitive problems
 - at-work concerns
 - body image
 - interaction with children
 - Medical Interaction
 - problems obtaining information from medical team
 - control of medical team
 - difficulty communicating with medical team
 - Marital
 - interactions with partner
 - affection with partner
 - communication with partner
 - neglect of care by partner

- overprotection by partner
- Sexual
 - sex interest
 - sexual dysfunction
- misc. subscales
 - chemotherapy related problems
 - radiation related problems
 - dating
 - compliance
 - economic barriers
- misc. items
 - ostomy
 - bladder control
 - frequent diarrhea
 - prosthesis
 - too much weight gain
 - diagnostic procedures painful
 - transportation

Mode of Administration: self or interview administered.

Administration Time: 20 minutes for the self-administration and 48 minutes for the comprehensive interview.

Time Frame: "During the past month including today"

Scoring: each problem statement is on a 0-4 scale with 0 being "not at all" and 4 being "very much." The most detailed level of scoring consists of 31 subscales and 7 misc. items. The 5 broader summary scales are generally used and a global score can be calculated.

Preference Based: No

Population Used In:

- in patients with breast cancer¹
- in adult survivors of lung, colon and prostate cancer²
- in Hispanic American patients (including those with low literacy rates)³

Reliability and Validity:

From Schag, et al. Assessing Problems...

- Test Retest Reliability: two correlations obtained for subscale scores and global overall scores: all correlations above .82
- Internal consistency: the mean α coefficients for all subscales was .81 and more than two-thirds of the subscales were above .80. The Overprotection by Partner subscale and the Neglect of Care by Partner had the lowest coefficients with .51 and .61. They are also the only two subscales to have 2 questions.

Validity:

- Pearson product-moment correlations were calculated.

- When the SCL-90 Overall Global Severity Distress Index increased, so did the number and severity of the problems measured by the CARES (formerly the CIPS).
- When the functional performance status in the KPS declined, physical problems increased
- As marital functioning declined, marital problems increased as measured by the DAS.

Comments:

- formerly "Cancer Inventory of Problem Situations"
- changes included disposing and rewording of a few questions but CIPS and CARES are generally the same, hence the validity for CIPS is still used for CARES today.
- a computerized scoring program is available.

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Ganz PA, Schag CAC, Lee JJ, Sim MS. The CARES: a generic measure of health-related quality of life for patients with cancer. *Qual Life Research* 1992: 19-29.

Schag CAC, Heinrich RL. Development of a comprehensive Quality of Life Measurement Tool: CARES. *Oncology* 1990; 4(5): 135-138.

Schag CAC, Heinrich RL, Aadland PA, Ganz PA. Assessing Problems of Cancer Patients: Psychometric Properties of the Cancer Inventory of Problem Situations. *Health Psychology* 1990; 9(1):83-102.

¹ Ganz PA; Hirji K; Sim MS, et al. Predicting psychosocial risk in patients with breast cancer. *Med Care* 1993 May;31(5):419-31.

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³ Canales S; Ganz PA; Coscarelli CA. Translation and validation of a quality of life instrument for Hispanic American cancer patients: methodological considerations. *Qual Life Res* 1995 Feb;4(1):3-11.

Cancer Rehabilitation Evaluation System-Short Form (CARES-SF)

Measure: CARES-SF

Contact Person: C. Anne Coscarelli Schag , Ph.D.
CARES Consultants
2210 Wilshire Boulevard, Suite 359
Santa Monica, CA 90403
Phone Number: (213) 450-7410

Terms of Use: Permission is needed and fees are required.

Disease Specific or General: Cancer General

Number of Questions: 59 problem statements and 10 screening questions. The first 36 questions are to be completed by all respondents while the subsequent questions are only answered by patients to whom the questions are applicable.

Domain: -Global Score as well as:

- Physical (10)
 - Ambulation (2)
 - Recreational activities (1)
 - Difficulty working (1)
 - Activities of daily life (2)
 - Pain (1)
 - Weight loss (2)
 - Clothing (1)
- Psychosocial (17)
 - Psychologic distress (3)
 - Worry (2)
 - Anxiety in medical situations (2)
 - Cognitive problems (1)
 - Body image (1)
 - At work concerns (3)
 - Difficulty communicating with friends/relatives (2)
 - Friends/relatives difficulty interacting (2)
 - Interaction with children (1)
- Medical Interaction (4)
 - Problems obtaining info from medical team (1)
 - Difficulty communicating with medical team (2)
 - Control of medical team (1)
- Marital (6)
 - Communication with partner (2)
 - Affection with partner (1)
 - Interaction with partner (1)
 - Overprotection by partner (1)
 - Neglect of Care by partner (1)
- Sexual (3)

- Sex interest (2)
- Sexual dysfunction (1)
- Miscellaneous subscales and items (19)
 - Chemotherapy-related problems (5)
 - Radiation related problems (2)
 - Dating (2)
 - Compliance (1)
 - Economic Barriers (3)
 - Ostomy (1)
 - Bladder control (1)
 - Frequent diarrhea (1)
 - Prosthesis (1)
 - Too much weight gain (1)
 - Transportation (1)

Administration Time: Average time 11 minutes (ranger from 2-45).

Mode of Administration: Self-Administration or interview.

Time Frame: “During the past month including today”

Scoring: Five-point scale ranging from 0 “not at all” to 4 “very much.” There is a single score, the Global-CARES-SF, as well as subscale scores.

Preference Based: No.

Population Used In:

- In African-American and white long term breast carcinoma survivors¹.
- In women with lung cancer. Measured by age, income level, and recurrence of disease.²
- In patients with prostate cancer³.
- In patients treated for metastatic kidney cancer⁴.

Reliability and Validity: (Data from Annals of Oncology on Dutch Patients)

Test/Retest Reliability:		<u>ICC</u>
	Physical:	.91
	Psychosocial:	.88
	Medical Interaction:	.80
	Sexual:	.76
	Marital:	.72
	Global:	.91
		<u>α</u>
Internal Consistency Reliability:	Physical T1	.84
	Physical T2	.87
	Physical T3	.86
TI-Before Treatment		
T2-one month later	Psychosocial T1	.81
T3-three months after T2	Psychosocial T2	.80
	Psychosocial T3	.82

Medical Interaction T1	.61
Medical Interaction T2	.73
Medical Interaction T3	.74
Sexual T1	.56
Sexual T2	.54
Sexual T3	.49
Marital T1	.64
Marital T2	.68
Marital T3	.65
Global T1	.89
Global T2	.90
Global T3	.90

Validity: Tested in two ways:

- The method of known group comparisons was used to assess the ability of the CARES-SF to distinguish between subgroups of populations in different clinical status.
- The responsiveness of the instrument to health status changes over time was assessed.

Comments:

- CARES-SF is highly related to CARES with $r = .98$.
- Because Dutch patients were subjects in the study used for validity and reliability data, the differences in reliability could be due to cultural differences. It is noted that Dutch patients may be less willing to report Sexual and Marital matters, thus contributing to the decreased internal consistency reliability in those areas.

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Center for Epidemiologic Studies Depression Scale

Measure: CES-D

Contact Person: Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Measurement 1977; 1:387. Copyright 1977 West Publishing Co./Applied Psychological Measurement.

Terms of Usage: No information available.

Disease Specific or General: Depression General

Number of Questions: 20 item questionnaire that consists of items taken from other depression scales.

Domain: Depression

- depressed mood
- feelings of guilt/worthlessness
- a sense of helplessness/hopelessness
- psychomotor retardation
- loss of appetite
- sleep disturbance

Administration Time: No data available.

Mode of Administration: Self-administration .

Time Frame: The past week including smaller time frames (ex.1-2days)

Scoring: 0-3 scale where 0 is "rarely or none of the time" and 3 is "most or all of the time" or reversed. Maximum score of 60 with a score over 16 indicating depression. A score of 22 is used in primary care settings.

Preference Based: No.

Population Used In:

- different ethnic and language status¹
- geriatric stroke patients²
- among Mexican Americans³
- urban elderly⁴
- elderly Puerto Rican population⁵
- elderly populations⁶
- low income mothers⁷
- Asian-Americans⁸
- young adolescents⁹
- Sex and age differences¹⁰
- Breast cancer patients on chemotherapy¹¹
- young Asian, black, and white women in America¹²
- gender bias¹³
- people with developing cancer¹⁴

- head and neck oncology patients¹⁵
- in stroke patients¹⁶
- in bone marrow transplant patients¹⁷
- in patients with breast cancer¹⁸
- in breast cancer survivors¹⁹

Reliability and Validity: From Weismann et al.:

- Correlations between the CES-D mean total scores and those of the Hamilton and Raskin Depression Scale, the self-report scale (SCL-90) were done with age, social scale, and sex in different populations
- Correlations between the CES-D total scores and factors in the SCL-90 in 5 psychiatric populations were done.

Validity:

- Concurrent validity shows that CES-D
 - “differentiated psychiatric patients from community normals”
 - “acutely depressed patients scored higher (more symptomatic) than other psychiatric patients.”
 - “Depressed subgroups within each of the three psychiatric populations (alcoholics, drug addicts, and schizophrenics) scored higher than not depressed patients within each of these populations.”
 - “Acutely depressed patients scored higher than recovered depressives.
 - “Correlations between the CES-D and other depression scales obtained by either self-report or by clinician interview were high.”
- Discriminant validity tests were performed. Low correlation of CES-D with variables such as age, social status, etc., were found as well as higher correlation of CES-D with the depression factor in the SCL-90 than other factors.

From Shinar, et al.

- inter-observer reliability-- $r=.74$

Comments:

- Not designed to provide a diagnosis of depression, rather measure symptoms of depression in community populations.
- The cut-off score of 16 is less useful than otherwise when applied to recovered depressives, as a large number of borderline cases were included.
- It is also less useful with drug addicted patients; there is a high false positive rate.
- The scale cannot distinguish between those subjects who have depressive symptoms in association with other medical and/or psychiatric problems, and those subjects who have depressive symptoms in the absence of such problems.

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FACIT-Functional Assessment of Chronic Illness Therapy (FACIT) Scales

Measure: Functional Assessment of Chronic Illness Therapy (FACIT) Scales; formerly Functional Assessment of Cancer Therapy (FACT) Scales

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Terms of Use: No charge to investigators willing to share applicable results, especially those results which further reliability and validity testing. Prior to including FACIT in a project, a *Project Information Form* must be completed. The new FACT manual and information on individual subscales may be purchased.

General or Disease Specific: The general form of the fact, FACT-G (27 items) can be further divided into cancer specific subscales:

		<u>Number of Items</u>
FACT-B-	For patients with Breast Cancer	9 + 27-->36
FACT-BI-	For patients with Bladder Cancer	12+27-->39
FACT-Br-	For patients with solid Brain Tumor	19+27-->46
FACT-C-	For patients with Colorectal Cancer	9+27--->36
FACT-CNS	For patients with cancer in the Central Nervous System	12+27-->39
FACT-Cx-	For patients with Cancer of the Cervix	15+27-->42
FACT-E	For patients with Esophageal cancer	17+27-->44
FACT-H&N-	For patients with Head and Neck cancer	11+27-->38
FACT-L-	For patients with Lung cancer	9 + 27-->36
FACT-O-	For patients with Ovarian cancer	12+27-->39
FACT-P-	For patients with Prostate cancer	12+27-->39
FACT-Pa	For patients with Pancreatic cancer	9+27--->36

Treatment specific subscales:

FACT-BMT-	For patients undergoing Bone Marrow Transplant	23+27--->50
FACT-CRA-	Modifiers and/or retinoid treatment	17+27--->44

FACT-ES-	For patients with Endocrine Symptoms	18+27--->45
FACT-NTX-	For patients with Neurotoxicity from systemic chemotherapy	11+27-->38
FACT-Taxane-	For patients with Taxane toxicity	16+27-->43

Symptom specific subscales:

FAACT-	Functional Assessment of Anorexia/Cachexia Treatment	18+27-->45
FACT-An-	For patients with anemia and/or fatigue	20
FACIT-F-	FACIT-Fatigue and the stand alone Fatigue Scale	13+27-->50
FAIT-F-	Functional Assessment of Incontinence Therapy- Fecal	12+27-->39
FAIT-U-	Functional Assessment of Incontinence Therapy-Urinary	11+27-->39

Non-cancer specific scales:

FACIT-Sp-	FACIT-Spiritual Well-Being	12+27-->39
FACIT-Pal-	FACIT-Palliative Care	19+27-->46
FAHI-	For patients with HIV Infection	47 total (44 scored)
FAMS-	Functional Assessment of Multiple Sclerosis	59 total (44 scored)
FANLT-	Functional Assessment of Non-Life Threatening conditions	26 total

Domains for FACT-G (Version 4):

- Physical Functioning (7 items)
- Social Well Being (7 items)
- Emotional Well Being (6 items)
- Functional Well Being (7 items)

Administration Time: 5 minutes for the FACT-G and varying time between 5-10 minutes for other scales most of which include the FACT-G

Mode of Administration: It is designed for patient self-administration but it may also be administered in an interview.

Time Frame: Past 7 days

Scoring: 0-4 scale with 0 representing a response of "not at all" and 4 representing a response of "very much." Maximum possible score on the FACT-G is 108 with a higher score indicating a high QoL.

Preference Based: No.

Population used in:

- Metastatic Prostate Cancer Among Men of Lower Socioeconomic Status¹
- Spanish FACT including use on people with low literacy skills.²
- Women and men with physical disabilities and cancer, and women with traumatic and women with chronic physical conditions.³
- In a rural sample.⁴
- After prostatectomy or radiation therapy.⁵
- Long term survivors of Cancer.⁶

Reliability and Validity: (Version 2)

FACT-G

	Test/Retest Reliability	Internal Consistency (α)	Spanish Fact-Internal Consistency (α)
Physical Well Being	.88	.82	.82
Functional Well Being	.84	.69	.83
Social Well Being	.82	.74	.74
Emotional Well Being	.82	.80	.66
Relationship with Doctor	.83	.65	.75
Total Score	.92	.89	.89

Note: Relationship with Doctor does not appear in version 4
Sensitivity to change studies have also been conducted

Validity:

w/ Functional Living Index-Cancer	$r=.80$
w/Quality of Life Index	$r=.74$
w/Taylor Manifest Anxiety Scale	$r=.57$
w/Brief Profile of Mood States	$r=.69$
w/Eastern Cooperative Oncology Group	$r=.56$

Comments:

-The FACT-G has been translated into 30 languages. Specific subscales have also been translated into other languages.

-Complete information on FACIT can be found at [http:// www.facit.org](http://www.facit.org)

-Changes from version 3 to version 4 of the FACIT include:

- dropping the Relationship with Doctor Subscale. This subscale was associated with ceiling effects.
- subscale weighted items are exclusion.
- item rewording.
- item numbering
- scoring

-FACIT is written at a sixth grade reading level.

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Functional Living Index-Cancer (FLIC)

Measure: FLIC

Contact Person: Dr. Harvey Schipper, M.D.
World Health Organization
Collaborating Centre for Quality of Life in Cancer Care
St.Boniface General Hospital Research Centre
351 Tache Avenue
Winnipeg, Manitoba
Canada R2H 2A6
Fax: Canada-(204)-235-1231

Terms of Usage: Contact above.

Disease Specific or General: Cancer General (22 questions)

Domain: designed to assess the overall quality of a patients day-to-day life

- vocational/activity (4)
 - work/household jobs (3)
 - leisure (1)
- affect/psychological activity (5)
 - anxiety and depression
- social interaction (2)
 - willingness to spend time with family and friends
- somatic sensation (3)
 - current health well-being
- subsidiary areas (8)
 - nausea (2),
 - pain or discomfort (2),
 - hardship due to cancer (3),
 - confidence in treatment (1)

Administration Time: Less than 10 minutes.

Mode of Administration: Self-administration.

Time Frame: -2 questions refer to "today"
-7 questions refer to "the past two weeks"
-1 question refers to "the past month"
-12 questions do not specify a time period

Scoring: Each of the 22 items has a Likert format linear analogue scale. Patients make a slash mark on the 7 evenly spaced integer scale according to their answer. The total score range is 22 to 154. Higher score = higher QoL. The FLIC was designed to be reported as a single score; however, subscores can be evaluated independently.

Preference Based: No.

Population Used In:

- in the elderly (acute myeloid leukemia)¹
- variable demography²
- women and men with physical disabilities and cancer, and women with traumatic and women with chronic physical conditions³
- in brain tumor patients⁴
- in patients with head and neck cancer⁵
- in breast cancer patients^{6,7}
- in patients with prostate cancer⁸
- in patients with colorectal cancer⁹
- in patients with pancreatic cancer¹⁰
- in patients with ovarian cancer¹¹
- in patients with lung cancer^{12,13}

Reliability and Validity:

Validation Tests: (from Shipper H et al.)

-Correlations of FLIC with concurrent validation tests:

Katz activities of daily living
General Health Questionnaire
 A scale: somatic symptoms
 B scale: anxiety and insomnia
 C scale: social dysfunction
 D scale: severe depression
 Total
Beck Depression
Karnofsky
Spielberger
 state anxiety
 trait anxiety
Melzack
 present pain index
 pain rating index

-Factor loadings on questions on the Sociability Factor, Family Situational Factor, and Nausea Factor were done for the different populations used in the study.

-In patients with advanced lung cancer there was a strong correlation between the FLIC score and physical status decline.

Comments:

- The Katz Activities of Daily Living did not correlate well with the FLIC. It is explained that the Activities of Daily Living Index is designed for those patients who are significantly more disabled than the population in the FLIC study. Thus, this may explain the ceiling effects that were observed in the Katz

Index.

-Currently available in 21 languages.

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Hospital Anxiety and Depression Scale

Measure: HADS

Contact Person: Susan Thompson
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2 Oxford Road East
Windsor
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UK

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Fax: 44-0-(1753)-856830

Terms of Usage: The cost for the HADS Complete Set is 40.25 pounds and may be obtained from Susan Thompson (above).

Disease Specific or General: Anxiety and Depression General

Number of Items: 14 items.

Domain: -Depression (7)
-Anxiety (7)

Administration Time: 2-6 minutes

Mode of Administration: Designed for self-administration though can be done through a trained health professional.

Time Frame: "in the past week"

Scoring: Each of the 14 items has a 0 to 3 scale with a maximum of 21 in each subscale and 42 overall. The authors of the scale recommend a 7/8 cutoff for possible and a 10/11 cutoff for probable anxiety or depression. They also proposed a 14/15 cutoff for severe depression.

Preference Based: No.

Population Used In:

- in Asian patients¹
- in patients with carcinoma of the cervix and vulva²
- in cancer patients receiving psychological treatment³
- in breast cancer patients at start of adjuvant radiotherapy. Relations to age and type of surgery⁴
- in Hodgkin's lymphoma out-patients⁵
- in patients with advanced breast cancer⁶
- in cancer patients^{7,17}
- in patients undergoing chemotherapy for small cell lung cancer⁸
- in cancer in-patients⁹
- in patients with lung cancer¹¹
- in bone marrow transplant recipients¹²

- in Chinese elderly¹³
- in patients with malignant melanoma¹⁴
- in long-term survivors of breast cancer¹⁵
- in the elderly¹⁶
- in head and neck cancer patients¹⁸
- in gastrointestinal cancer patients¹⁹
- in female lung transplant candidates and recipients²⁰
- in patients with colorectal liver metastasis²¹
- in patients with advanced colorectal cancer²²
- in adolescents with cancer²³
- in men with prostate carcinoma²⁴
- in patients with testicular cancer²⁵

Reliability and Validity: (From Hermann)

Reliability:

- Internal consistencies are acceptable at α s of .80 to .93 for the anxiety subscale and .81-.90 for the depression subscale.
- Test retest reliability: $r > .80$ after up to 2 weeks, decreasing over longer time periods.

Discriminant and concurrent validity:

- mean correlation between the anxiety and the depression subscale is $r = .63$.
- construct validity and treatment validation studies were reviewed in Hermann.

Comments:

- the HADS has been found not to identify a specific form of drug depression.
- the HADS cannot be used to make a diagnosis of major depressive disorder.
- HADS is available in over 30 languages.

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Health Utilities Index

Measure: Health Utilities Index (HUI)

Contact Person: William Furlong
Health Utilities Inc.,
88 Sydenham Street, Dundas, Ontario
L9H 2V3 Canada
Phone number: (905) 525-9140 ext.22389
Fax number: (905) 627-7914
e-mail: furlongb@mcmaster.ca

Terms of Use:

Disease Specific or General: General

Number of Items: Mark II: 7 Mark III: 8

Domain: Mark II:

- Sensation
- Mobility
- Emotion
- Cognition
- Self-care
- Pain
- Fertility

Mark III:

- Vision
- Hearing
- Speech
- Ambulation
- Dexterity
- Emotion
- Cognition
- Pain

Mode of Administration: Self-administered and interview administered versions are available.

Administration Time:

Scoring:

Time Frame:

Preference Based: Yes.

Population Used In:

-different gender, age, family structure, main activity, education, occupation, income, social support,

smoking behaviour, drinking behaviour, weight, and physical activity¹
-in pediatric oncology patients²
-in brain tumor patients³

Reliability and Validity:

Comments:

References:

1. Denton M, Walters V. Gender differences in structural and behavioural determinants of health: an analysis of the social production of health. Soc Sci Med 1999 May; 48(9): 1221-35.
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Impact of Event Scale

Measure: IES

Contact Person: Mardi Horowitz
mardi@itsa.ucsf.edu

Terms of Use: Contact above.

General or Disease Specific: Specific Event

Number of Items: 15

Domain: -posttraumatic intrusion (7)
-posttraumatic avoidance (8)

Administration Time: Self-administered

Mode of Administration: No time given though should take 5 minutes.

Time Frame: "During the past 7 days"

Scoring: There are four choices for each item which are weighed from 0-5 with 0 representing "not at all" and 5 representing "often." Lower scores represent lower impact of the event. There are two subscale scores for the two domains and an overall score.

Preference Based: No.

Population Used In:

- in bladder cancer notification¹
- in cancer patients with advanced disease²
- recurrent cancer patients³⁴
- in patients with operable breast cancer⁵
- in women tested for the BRCA1 mutation⁶
- in women attending for genetic counseling⁷
- in survivors of Hodgkin's disease⁸
- in patients with prostate cancer⁹
- in patients with gastrointestinal cancer¹⁰
- in recently diagnosed breast cancer patients¹¹
- in different races (Caucasian, African Americans, and Hispanics)¹²

Reliability and Validity: (from Biere et al.)

Reliability:

-The IES total score had an alpha coefficient of .94; the avoidance and intrusion subscales each had an alpha of .90.

Validation:

-An incremental validity analysis with respect to trauma history was done by entering IES Intrusion and Avoidance scales into a regression equation. The IES scores did not predict

additional post traumatic event variance when compared to two different instruments (Los Angeles Symptom Checklist Arousal scale and Trauma Symptom Inventory scales).

Comments:

- There were no significant difference in IES scores between men and women.
- African Americans and Hispanics had higher IES scores than Caucasians for the total score (20.9, 20.1 and 12.8), intrusion score (9.9, 10.0, 6.3), and Avoidance score (11.0, 10.1, 6.5).

References:

Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: A Measure of Subjective Stress. *Psychosomatic Medicine* 1979; 41(3):209-218.

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Karnofsky Performance Status Scale

Measure: KPS

Contact Person: N/A

Terms of Use: N/A

General or Disease Specific: Cancer General (though can be used in other diseases)

Number of Items: One scale

Domain: Functional Status

Administration Time: The interviewer has to be able to collect necessary information to gain an overall understanding of the subject's health.

Mode of Administration: Clinical Assessment

Time Frame: Current

Scoring: 0-100 scale. 100 represents normal functioning and 0 represents death.

Preference Based: No

Population Used In: (Note: this is a sampling of populations used in from 1995-1999. The Karnofsky Performance Status Scale is so widely used that individual medline searches need to be conducted)

- in patients with pancreatic cancer¹
- in patients with advanced stage head and neck cancer²
- in elderly patients with advanced non-small-cell lung cancer³
- in medically inoperable stage I endometrial cancer patients⁴
- in advanced colorectal cancer patients⁵
- in patients with advanced lung cancer⁶
- different genders⁷
- in patients over the age of 65⁸
- in women with advanced lung cancer⁹
- in brain tumor patients¹⁰
- in lung cancer¹¹
- in brain cancer¹²
- in patients with central nervous system lymphoma¹³
- in women with ovarian cancer¹⁴

Comments:

- although originally only used with cancer patients, the KPS can be applicable to a multitude of conditions and diseases.
- widely used as an outcome measure to compare differences in abilities of patients both before and after a treatment intervention.

References:

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Mental Health Inventory

Measure: MHI and MHI-5

Contact Person:

Terms of Use:

General or Disease Specific:

Number of Items: 38 in the MHI, 5 in the MHI-5

Domain:

- Psychological Distress
 - anxiety
 - depression
 - behavior/ emotional control
- Psychological Well-Being
 - general positive affect
 - emotional ties

(note: the MHI-5 does not have an emotional ties items. Rather, it has two general positive affect items)

Administration Time:

Mode of Administration:

Time Frame:

Scoring:

Preference Based:

Population Used In:

Reliability and Validity:

Comments:

References:

Memorial Symptom Assessment Scale

Measure: MSAS

Contact Person: Russell K. Portenoy, M.D.

Dept. of Pain Medicine and Palliative Care
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NEW YORK, N.Y. 10003
USA

Telephone: 212-844-8370

Fax: 212-844-1503

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Terms of Use: contact the above.

General or Disease Specific: Cancer General

Number of Items: 32

Domain: Note: the Global Distress Index is the average of the frequency of four psychological symptoms and six physical symptoms. Therefore, the symptoms also appear in the other subscales.

-Global Distress Index

- feeling sad
- worrying
- feeling irritable
- feeling nervous
- lack of appetite
- lack of energy
- pain
- feeling drowsy
- constipation
- dry mouth

-Physical Symptom subscale

- lack of appetite
- lack of energy
- pain
- feeling drowsy
- constipation
- dry mouth
- nausea
- vomiting
- change in taste
- weight loss
- feeling bloated
- dizziness

-Psychological Symptom Subscale (6)

- worrying
- feeling sad
- feeling nervous
- difficulty sleeping
- feeling irritable
- difficulty concentrating

Administration Time: Not available

Mode of Administration: Self-administered

Time Frame: "During the past week"

Scoring: 24 scores are evaluated in terms of frequency (4 pt. scale), severity (4 pt. scale), and distress (5 pt. scale), while 8 scores are evaluated only in terms of severity and distress. The psychological subscale score is an average of the symptom scores for the 6 psychological symptoms. The physical subscale is likewise an average of its 12 symptom subscales. The Global Distress Index is the average of the single dimension scores for 10 symptoms and the total MSAS score is the average score of the 32 symptom scores.

Preference Based: No

Population Used In:

- in patients breast cancer patients who received a bone marrow transplant¹
- for pain measurement in patients with metastatic breast cancer²
- in women with ovarian cancer³⁴
- in patients with advanced breast cancer⁵

Reliability and Validity:

(from Portenoy et al.)

Internal consistency:

-Cronbach alpha coefficients were:

- .88 for the group of patients with a high prevalence of physical symptoms.
- .83 for the group of patients that had psychological symptoms
- .53 for the group of patients with a low prevalence of physical symptoms.

Validity:

- the correlation between mean severity and mean frequency scores across symptoms was $r=.80$
- the correlation between mean severity and mean distress scores across symptoms was $r=.70$
- the correlation between mean frequency and mean distress scores across symptoms was $r=.43$

validity of score:

- The Psychological subscale was broken down into EMOT (emotional state) and CONC (related to concentration). The PHYS H (see internal consistency) was broken down into PAIN TREAT (symptoms associated with pain and treatment) and GASTR (gastrointestinal symptoms). A factor analysis of variance graph was made (see figure 2 portenoy et al.)
- the strongest association between MSAS and an overall measure of QoL was the FLIC- Functional Living Index Cancer. Other scales measured include RAND well-being, RAND distress, KPS, and Mood VAS.

Comments:

N/A

References:

Chang VT, Thaler HT, Polyak TA, et al. Quality of Life and Survival: The Role of Multidimensional Symptom Assessment. *Cancer* 1998; 83(1): 173-179.

Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics, and distress. *European Journal of Cancer* 1994. 30A(4): 1326-1336.

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Profile of Mood States

Measure: POMS and POMS Short Form

Contact Person: EdITS/Educational and Industrial Testing Service
P.O. Box 7234
San Diego, California 92167
Phone: (619) 222-1666 (800) 416-1666
Fax: (619) 226-1666
email: edits@k-online.com

Terms of Use: Prices range from \$9.50 for a packet of 25 to \$143.50 for a packet of 500. Instrument usage restricted to Ph.Ds.

Domain: -Tension-Anxiety
-Depression-Dejection
-Anger-Hostility
-Vigor-Activity
-Fatigue-Inertia
-Confusion-Bewilderment

Number of Items: 65 for the POMS, 30 for the POMS Short Form

Administration Time: 3-5 minutes for the POMS, 1-3 minutes for the POMS Short Form

Mode of Administration: self-administered

Time Frame: "during the past week"

Scoring: Each of the 65 adjectives are scores on a 0 to 4 scale with 0 representing "not at all" and 4 representing "extremely." Scores for each factor are the sum of items in that subscale. An overall score can also be obtained.

Preference Based: No

Population Used In:

- in women newly diagnosed with breast cancer¹
- in adult and geriatric population- age-, gender-, and race- stratified²
- in older adults³
- in middle aged women⁴
- in gynecological cancer patients⁵
- in ambulatory lung cancer patients⁶
- in patients with advanced breast cancer⁷
- in patients with metastatic breast cancer⁸
- in women with breast cancer⁹
- in patients undergoing primary breast cancer treatment¹⁰
- in patients with small-cell lung cancer¹¹
- in patients with lung cancer¹²
- in bone marrow transplant recipients¹³
- in early-stage prostate cancer patients¹⁴

-in newly diagnosed malignant melanoma patients¹⁵

Reliability and Validity:

(from Norcross et al.)

Internal Consistency:

	<u>alpha coefficients</u> (from two different population)	
Tension-Anxiety	.92	.91
Depression-Dejection	.95	.94
Anger-Hostility	.93	.92
Vigor-Activity	.91	.91
Fatigue-Inertia	.93	.93
Confusion-Bewilderment	.86	.84

(from Spilker et al.)

-“Test re-test coefficients in a sample accepted for psychiatric treatment ranged from $r=.65$ for vigor to $r=.74$ for depression for a median time of 20 days. Correlations of scores following 6 weeks of treatment were much lower (123).”

(from Little et al.)

-The POMS demonstrated concurrent validity “in appropriately detecting diagnostic differences, clinical setting differences, and clinical change (46).”

-factor loading were performed on each domain with different categories. Loading scores were relatively high (Norcross et al. 1272)

Note: Reliability and Validity results could not be located for the POMS-Short Form

Comments:

-Age range: 18-adult

-In addition to the long form and the short form, there is also a bi-polar form.

References:

Little K, Penman E. Measuring Subacute Mood Changes Using the Profile of Mood States and Visual Analogue Scales. *Psychopathology* 1989; 22: 42-49.

Norcross JC, Guadagnoli E, Prochaska JO. Factor Structure of the Profile of Mood States (POMS): Two Partial Replications. *J Clin Psychology* 1984; 40(5): 1270-1277.

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 15. **Fwzy NW.** A psychoeducational nursing intervention to enhance coping and affective state in newly diagnosed malignant melanoma patients. *Cancer Nurs* 1995 Dec;18(6):427-38.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items (QLQ-C30) + Supplemental Specific Modules

Measure: EORTC-QLQ-C30 + specific modules

Contact Person: EORTC Data Center
Quality of Life Unit
Ave.E.Mounier 83, Bte 11
B - 1200 Brussels
Belgium

Phone Number: 31-20-512-2481

Fax Number:: Belgium-(2)-7723545

Terms of Use: Written consent prior to use is required. If the instrument is used in a university-based investigation, it is free. Other uses are subject to royalty fees.

Disease Specific or General: EORTC-QLQ-C30 is cancer general but is designed to be used with a supplementary specific module (many modules are still under development).

QLQ-BR23-breast cancer module (23)
QLQ-LC13- lung cancer module (13)
QLQ-BN20- brain cancer module (20)
QLQ-CR38- colorectal cancer module (38)
QLQ-H&N35-head and neck cancer module (35)
QLQ-OE24-oesophageal cancer module (24)
QLQ-OV28-ovarian cancer module (28)
QLQ-S- survivors (45)
Bladder cancer module
Myeloma module
Pancreatic cancer module
Body Image module
High-dose Chemotherapy module
Leukemia module
Ophthalmic cancer module
Palliative care module
prostate cancer module

Domain: QLQ-C30 has 9 subscales.

6 functional scales: -physical
-role
-cognitive
-emotional
-social
-global QoL

3 symptom scales: -fatigue
-pain
-nausea and vomiting

+ single items assessing additional symptoms (dyspnea, sleep disturbance, constipation, diarrhea and financial impact).

Preference Based: No.

Mode of Administration: Self or interview administered.

Administration Time: 11 to 12 minutes for the QLQ-C30. No data available on the modules.

Time Frame: 7 questions are general time period questions, and 23 are "during the past week."

Number of Items: 30 items in the QLQ-C30. The modules vary in length.

Scoring: Separate scores are calculated for the 9 subscales as well as the individual items. The scores can then be linearly transformed on a 0-100 scale with a higher score indicating higher QoL.

Reliability and Validity:

Reliability (from Aaronson et al.):

Internal Consistency:

	Before Treatment	After Treatment
Physical	.68	.71
Role	.54	.52
Cognitive	.56	.73
Emotional	.73	.80
Social	.68	.77
Global quality of life	.86	.89
Fatigue	.80	.85
Nausea and vomiting	.65	.73
Pain	.82	.76

Validity:

- inter-scale correlations: the strongest correlations occurred between the physical functioning, role functioning, and fatigue scales (.54 to .63). Considerable correlations were also found between the fatigue, emotional, and social functioning scales (>.40). A weak correlation was found between the emotional functional scale and the physical and role functioning scales.

-Clinical Validity was also evaluated in terms of responsiveness to change in health status and known-group comparisons.

From McDowell et al.:

-the emotional functional scale correlated .71 with the Hospital Anxiety and Depression Scale.
-the physical functional scale correlated .73 with the Sickness Impact Scale, with a .58

correlation with the cognitive and fatigue scales, .55 with the role scale, and .48 with the emotional and social scales.

-with the CARES, there was a .71 correlation with the physical scales, a .56 with the emotional scales, .46 with the social scale, and .69 with the pain scale.

-the QLQ-C30 has also been compared with other instruments.

Population Used In:

- in patients with nonmetastatic breast carcinoma¹
- in gastric cancer patients²
- in patients with localized prostate cancer³
- for patients with multiple myeloma⁴
- in head and neck cancer patients⁵
- in Hodgkin's disease⁶
- in patients 70 and older with advanced non-small-cell lung cancer⁷
- in people with different age and gender⁸
- in patients with breast cancer^{9,10}
- in patients with esophageal cancer¹¹
- in patients with prostate cancer¹²
- in patients with brain cancer¹³
- in leukemia patients¹⁴
- in patients with malignant melanoma¹⁵
- in patients with lung cancer¹⁶
- in patients with ovarian cancer¹⁷
- in advanced colorectal cancer¹⁸

Comments:

-available in over 30 languages

-the weakest scale from a psychometric viewpoint was the role functioning scale.

It has been suggested that because it is a brief scale and limited to work and household activities, it should be expanded to a broader range of activities thus lending to a more variable range of responses.

-There are some reservations concerning the QLQ-C30s ability to discriminate between patients with different stages of disease though the manner in which this was determined may not be particularly useful predictor of current functioning levels (see Aaronson et al).

-The website <http://www.eortc.be/home/qol/> has information about the QLQ-C30 plus an order form to order a reference values manual and CD ROM.

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Quality-Adjusted Time Without Symptoms of disease and Toxicity of treatment

Measure: Q-TWiST

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Terms of Use: N/A

General or Disease Specific: Cancer and AIDS General

Number of Items: N/A

Domain: Utility Instrument that makes comparisons in quality and quantity of life.

Administration Time: N/A

Mode of Administration: N/A

Time Frame: General

Scoring: (from Gelber et al.) "A weight of 0 indicates the period of time is as bad as death, and a weight of 1 indicates perfect health. Weights between 0 and 1 indicate degrees between these extremes. . .The Q-TWiST end point is obtained by adding the weighted periods of time (74)."

Preference Based: Yes.

Population Used In:

- in patients with metastatic prostate cancer¹
- in advanced prostate cancer²
- in patients undergoing treatment with Interferon³
- adjuvant therapy of patients with melanoma⁴
- adjuvant chemotherapy for breast cancer⁵⁶
- in patients with node-positive breast cancer⁷
- in operable breast cancer⁸
- in patients undergoing adjuvant radiation therapy and chemotherapy for resectable rectal cancer⁹
- in postmenopausal breast cancer¹⁰
- in patients with stage III colon cancer¹¹
- in small cell lung cancer¹²

Reliability and Validity: N/A

Comments:

- The Q-TWiST "is a statistical methodology designed to facilitate treatment comparisons highlighting quality-of-life oriented tradeoffs (Gelber in an email)."
- Can compare treatments in terms of QoL outcomes and in terms of survival.
- Formulas provided in Gelber et al, 1996.
- One of the biggest advantages that Q-TWiST has is that the results can be presented as threshold analysis in graphs or table of the weights of two treatments.
- The main disadvantage of Q-TWiST is that weights are assigned to a small number of discrete states.

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The Quality of Well-Being Scale

Measure: QWB

Contact Person: Medical Outcomes Trust
8 Park Plaza, #503
Boston, MA 02116-4313
USA

Phone: (617)-426-4046

Fax: (617)-426-4131

Email: MOTrust@worldnet.att.net

Terms of Use: \$69.00. Contact MOS Trust for more details.

General or Disease Specific: General

Number of Items: The interview administered version is relatively long and complex, with the length depending on the necessary branching that occurs when questions are answered in a certain manner. Additionally, patients are classified according to their most undesirable symptom complex out of 27. The self administered QWB is an 80 –82 item instrument.

Domain:

- mobility
- physical activity
- social activity
- symptom/ complex

Mode of Administration: self or interview administration

Administration Time: 15-35 minutes for the interview administration. 10 minutes for the QWB-SA, the self-administered instrument.

Time Frame: For the self-administered: “in the last three days, not including today” For the interview administered: in each day of the previous week.

Scoring: A formula taking into account the weighted scoring is used. There is a 0 to 1 scale with 0 representing death and 1 representing complete well being.

Preference Based: Yes

Population Used In:

- patients undergoing chemotherapy for small cell lung cancer¹
- in patients with cancer of the cervix²
- in pediatric oncology patients³
- in patients with asymptomatic prostate nodules in primary care⁴
- in healthy older adults (comparing health status measurements)⁵
- in older adults⁶
- in lung transplant patients⁷
- in male HIV patients⁸

- in an inner-city population⁹
- in patients with major depression¹⁰
- in populations with different gender, race, and social class (w/ arthritis)¹¹
- in late life psychosis¹²
- in patients with serious illnesses including Cancer and AIDS¹³

Reliability and Validity:

Reliability: (from Anderson et al.)

- interday correlation coefficients ranged from .78 to above .99 with only one under .80 and most above .99.
- interday agreement percentage reliability ranged from .77 to 1.0 with the majority being over .80.

Validity: (from Kaplan et al.)

- correlations between QWB scores and number of reported symptoms: -.075
- correlations between QWB scores and number of chronic health problems: -.96

-specific validity studies for pediatric oncology patients, patients with cystic fibrosis, AIDS, etc. Run Medline Search for more studies.

Comments:

- quality control is often an issue as every interviewer administers the QWB in a different manners
- criticisms of the QWB include difficulty and length of administration compared to other instruments such as the SF-36.

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Rotterdam Symptom Checklist

Measure: RSCL

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The Netherlands

Terms of Use: permission is required from the above.

General or Disease Specific: Cancer General

Number of Items: 38 item checklist

Domain: -30 item symptom checklist
 -physical
 -psychosocial
 -8 items referring to activities of daily living
 -1 item asking about overall quality of life

Administration Time: 8 minutes

Mode of Administration: self-administration

Time Frame: "during the past week"

Scoring: Items are completed by checking off the appropriate box; "not at all," "a little," "somewhat," or "very much." These responses are converted to a 1-4 scale. Individual evaluations are made for physical distress, activity level, and psychological distress.

Preference Based: No

Population Used In:

- in women with early breast cancer¹
- in women with advanced breast cancer²
- in patients with lung cancer³
- in patients with advanced or end-stage cancer⁴
- in patients receiving radiotherapy⁵
- in patients with advanced colorectal cancer⁶
- a cross-cultural population⁷
- in a Spanish speaking population⁸
- in adolescents with cancer⁹
- in patients with testicular cancer¹⁰
- in pediatric oncology patients¹¹
- in patients with ovarian cancer¹²
- in patients with esophageal carcinoma¹³
- different sex and age groups¹⁴

Reliability and Validity:

(from de Haes JC, et al. and Agra et al. for the Spanish version)

Internal consistency:

- reliability for the physical distress scale ranged from .68 to .85 for the baseline measurement and .77 to .85 after three months from original measurement
- the range was from .57 to .80 for the activities scale for the baseline and .41 to .89 at the three month measurement
- for the psychological subscales, the reliability ranged from .83 to .89 for the first measurement and .85 to .90 for the three month measurement

Spanish version reliability:

- α coefficients ranged from .74 (physical) to .90 (activity).
- twenty-four hour test-retest intraclass correlation coefficient ranged from .71 to .88.

Validity:

- factor loadings on two factor solution at baseline assessment were conducted for each of the 27 symptoms
- cross-cultural comparisons were done for physical distress, activity level, psychological distress, and overall QoL. Comparisons indicated that patients enter trials with different distress levels depending on their culture. Activity level, psychological distress, and overall QoL also showed differences in culture from baseline to three months.

Comments:

- it is possible to include symptoms for specific groups of cancer patients or treatment regimens in the RSCL.
- available in 10 languages.

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Symptom Checklist 90- Revised (SCL-90)

Measure: SCL-90R-Formerly the Hopkins Symptom Checklist 90

Contact Person: National Computer Systems, Inc.
1-800-627-7271, ext. 5151
email: assessment@ncs.com

Terms of Use: The instrument is copyrighted and a fee of 28 dollars is required for the manual. For copies of the instrument, the price of scoring, either hand scored, profiled, or an interpretive report is included. \$36 dollars is the beginning price.

General or Disease Specific: General Psychological.

Number of Items: 90

Domain:

General Indices:

- Global Severity Index (GSI)
- Positive Symptom Distress Index (PSDI)
- Positive Symptom Total (PST)

Primary Symptom Dimensions:

- Somatization (SOM)
- Obsessive-Compulsive (OC)
- Interpersonal Sensitivity (INT)
- Depression (DEP)
- Anxiety (ANX)
- Hostility (HOS)
- Phobic Anxiety (PHOB)
- Paranoid Ideation (PAR)
- Psychotism (PSY)

Administration Time: 12-15 minutes

Mode of Administration: Self-administration

Time Frame: "during the past week, including today."

Scoring: Each item is based on a 0-4 scale with 0 being "not at all" bothered and 4 representing "extremely" bothered. Ratings on the items that make up a given scale are summed and then divided by the number of items rated. Higher scores indicate higher emotional distress.

Preference Based: No.

Population Used In:

- in older women¹
- in black, Hispanic, and white outpatients²
- in a mixed geriatric group³
- in patients who had a mastectomy⁴

- in patients with advanced breast cancer⁵
- in young adult psychiatric patients⁶
- in early breast cancer⁷
- in newly diagnosed breast cancer patients⁸
- in patients with chemotherapy induced side effects⁹
- in cancer patients with anxiety and depressive symptoms¹⁰
- in adolescent and young adult survivors of pediatric malignancy¹¹
- in patients suffering from breast and gastrointestinal cancer¹²
- in women with stage II breast cancer¹³
- in male and female populations¹⁴

Reliability and Validity:

- an information packet is being sent with necessary information.

Comments:

- The SCL-90 was the precursor to the SCL-90-R. The former of the two was flawed in its Anxiety scale and its Obsessive-Compulsive scale.
- Computer-generated reports can be obtained for the SCL-90-R.
- Appropriate for ages 13 and older.
- Written on a 6th grade reading level.
- More information can be found at: <http://assessments.ncs.com>

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⁸ **Roberts CS, Cox CE, Reintgen DS, et al.** Influence of physician communication on newly diagnosed breast patients' psychologic adjustment and decision-making. *Cancer* 1994 Jul 1;74(1 Suppl):336-41.

⁹ **Morrow GR.** Behavioural factors influencing the development and expression of chemotherapy induced side effects. *Br J Cancer Suppl* 1992 Dec;19:S54-60; discussion S60-3.

¹⁰ **Holland JC, Morrow GR, Schmale A, et al.** A randomized clinical trial of alprazolam versus

progressive muscle

relaxation in cancer patients with anxiety and depressive symptoms. *J Clin Oncol* 1991 Jun;9(6):1004-11.

¹¹ **Ikin TD, Phipps S, Mulhern RK, Fairclough D.** Psychological functioning of adolescent and young adult survivors of pediatric malignancy. *Med Pediatr Oncol* 1997 Dec;29(6):582-8.

¹² **Bastecky J, Tondlova H, Vesela J, et al.** Prevalence of psychopathology in patients suffering from breast and gastrointestinal cancer. *Patient Educ Couns* 1996 Jul;28(2):175-8.

¹³ **Tross S, Herndon J 2nd, Korzun A, et al.** Psychological symptoms and disease-free and overall survival in women with stage II breast cancer. *Cancer and Leukemia Group B. J Natl Cancer Inst* 1996 May 15;88(10):661-7.

¹⁴ **Carpenter KM, Hittner JB.** Dimensional characteristics of the SCL-90-R: evaluation of gender differences in dually diagnosed inpatients. *J Clin Psychol* 1995 May;51(3):383-90.

The Symptom Distress Scale

Measure: SDS

Contact Person: Ruth McCorkle

Professor

Yale University

School of Nursing

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fax: 203-737 2414

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Terms of Use: Contact the above for permission.

General or Disease Specific: Cancer specific and heart disease

Number of Items: 13

Domain:

- Nausea (2)
- Appetite
- Insomnia
- Pain (2)
- Fatigue
- Bowel
- Concentration
- Appearance
- Breathing
- Outlook
- Cough

Administration Time: 5 minutes

Mode of Administration: self-administered

Time Frame: general time frame

Scoring: Scores of 1 to 5 are circled for statements in each item with 1 representing "low distress" and 5 representing "high distress." Scores are then added up for a range of 13 to 65.

Preference Based: No

Population Used In:

- in patients with recurrent cancer (variable demographics and illness variables)¹
- in advanced cancer patients in a home care program²
- in black patients (included demographic data)³
- in women with lung cancer⁴⁵
- adults with acute leukemia in remission⁶

- in patients undergoing chemotherapy and radiotherapy⁷
- in women with advanced breast cancer⁸
- in patients with metastatic breast cancer undergoing chemotherapy (with 5-fluorouracil)⁹

Reliability and Validity:

internal consistency:

- the manual gives Cronbach Alpha Reliability's for 47 studies. The range is from .70 for various types of cancer to .92 for HIV infection. Most studies had alphas above .80.

Spanish version internal consistency:

- coefficient alphas were found for Hispanic monolingual and Hispanic bilingual Spanish speakers in two different geographic locations (San Antonio, and Los Angeles). Coefficients ranged from .73 to .93.

validity:

- concurrent validity studies between SDS and other instruments can be found in the manual.

Comments:

- available in English, Spanish, French, and Swedish.
- www.qlmed.org/SDS has links to the SDS manual and instrument.
- there has not been an identification of a cut-off score

References:

McCorkle R, Quint-Benoliel J. Symptom distress, current concerns, and mood disturbance after diagnosis of life-threatening disease. *Soc. Sci. Med* 1983; 17(7):431-438.

McCorkle R, Cooley ME, Shea JA. A user's manual for the Symptom Distress Scale. (Accessed at www.qlmed.org/SDS)

¹ **Taylor EJ.** Factors associated with meaning in life among people with recurrent cancer. *Oncol Nurs Forum* 1993 Oct;20(9):1399-405; discussion 1406-7.

² **Peruselli C, Camporesi E, Colombo AM, et al.** Quality-of-life assessment in a home care program for advanced cancer patients: a study using the Symptom Distress Scale. *J Pain Symptom Manage* 1993 Jul;8(5):306-11.

³ **O'Hare PA, Malone D, Lusk E, McCorkle R.** Unmet needs of black patients with cancer posthospitalization: a descriptive study. *Oncol Nurs Forum* 1993 May;20(4):659-64.

⁴ **Sarna L.** Correlates of symptom distress in women with lung cancer. *Cancer Pract* 1993 May-Jun;1(1):21-8.

⁵ **Sarna L, Brecht ML.** Dimensions of symptom distress in women with advanced lung cancer: a factor analysis. *Heart Lung* 1997 Jan-Feb;26(1):23-30.

⁶ **Evans DR, Thompson AB, Browne GB, et al.** Factors associated with the psychological well-being of adults with acute leukemia in remission. *J Clin Psychol* 1993 Mar;49(2):153-60.

⁷ **Holmes S.** Preliminary investigations of symptom distress in two cancer patient populations: evaluation of a measurement instrument. *J Adv Nurs* 1991 Apr;16(4):439-46.

⁸ **Coward DD.** Self-transcendence and emotional well-being in women with advanced breast cancer. *Oncol Nurs Forum* 1991 Jul;18(5):857-63.

⁹ **Chu L, Sutton LM, Peterson BL, et al.** Continuous infusion 5-fluorouracil as first-line therapy for metastatic breast cancer. *J Infus Chemother* 1996 Fall;6(4):211-6.

Medical Outcomes Study 12-Item Short Form (SF-12) Health Survey

Measure: SF-12

Contact Person: QualityMetric Inc.
640 George Washington Highway,
Suite 201
Lincoln, RI 02865
Phone: (401)334-8800
(888) 947-9800
FAX: (401) 334-8801
Email: info@qmetric.com

The Health Assessment Lab
750 Washington Street
Boston, MA 02111
Phone: (617)636-8098
(800) 572-9394
FAX: (617) 636-8077

Terms of Use: : Permission to use the SF-12 is granted royalty free for institutional non-commercial use and for individual research. Organizations who wish to distribute the SF-12 or scoring algorithms as part of their product need to email: license@qmetric.com.

General of Disease Specific: General

Number of Items: 12

Domains:

- Physical Component Summary (6)
 - Physical Functioning
 - Role-Physical
 - Bodily Pain
 - General Health
- Mental Component Summary (6)
 - Vitality
 - Social Functioning
 - Role-Emotional
 - Mental Health

Administration Time: 2 minutes or less

Mode of Administration: self, computer, interview, or mail administration.

Time Frame: 9 items refer to the "past 4 weeks" while 3 questions are general time items.

Scoring: The SF-12 uses algorithms that involve weighted item responses. There is a computer disk with the scoring codes and a test dataset for checking scoring accuracy. Both are found in the manual.

Preference Based: No

Population Used In:

- in an inner-city population¹
- in nine European countries (Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) and across different age groups²
- in patients with head and neck cancer³
- in different gender and age populations⁴

Reliability and Validity: (from Ware et al. 1996)

-Test retest reliability:

PCS-12

890 in the United States

.760 in the United Kingdom

MCS-12

.760 in the United States

.774 in the United Kingdom

-85.3% scored at the second administration within 95% confidence intervals of the first administration scores

Validity:

-Relative validity coefficients were calculated for summary measures in terms of "Serious Physical vs. Minor Medical" and "Serious Physical and Mental vs. Mental only"

PCS-12 RV: .93 and .63

PCS-36 RV: .97 and .72

MCS-12 RV: .03 and .11

MCS-36 RV: .06 and .10

-mental health validity tests were done in terms of "Mental vs. Minor Medical" and "Serious Mental and Physical vs. Serious Physical Only"

PCS-12 RV: .01 and .03

PCS-36 RV: .02 and .03

MCS-12 RV: 1.07 and .60

MCS-36 RV: 1.12 and .62

Comments:

-SF-12 is an alternative to the SF-36 when large samples are used and when the goal is to monitor overall physical and mental health outcomes.

-The SF-12 compromises validity because the subscales only have one or two items each

-Available in over 25 languages

References:

Ware JE Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Medical Care* 1996; 34(3): 220-233.

¹ **Jacobson JW, McNutt RA.** Implementing the SF-12 in an inner-city clinic: the importance of providing help. *Int J Qual Health Care* 1998 Aug;10(4):355-6.

² **Gandek B, Ware JE, Aaronson NK, et al.** Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *International Quality of Life Assessment. J Clin Epidemiol* 1998 Nov;51(11):1171-8.

³ **Terrell JE, Nanavati KA, Esclamado RM, et al.** Head and neck cancer-specific quality of life: instrument validation. *Arch Otolaryngol Head Neck Surg* 1997 Oct;123(10):1125-32.

⁴ **Lundberg L, Johannesson M, Isacson DGL, Borgquist L.** The Relationship between Health-state Utilities and the SF-12 in a General Population. *Medical Decision Making* 1999; 19(2):128-140.

Sickness Impact Profile

Measure: SIP and Short Form

Contact Person: Medical Outcomes Trust
PMB #503
198 Tremont Street
Boston, MA 02116-4705
Phone: (617) 426-4046
Fax: (617) 426-4131
email: MOTrust@worldnet.att.net

Terms of Use: A charge of \$160 covers the manual and instrument.

General or Disease Specific: Disease general

Number of Items: 136 (Short Form 68)

Domain: Physical (45)
-ambulation (12)
-mobility (10)
-body care and movement (23)

Psychosocial (48)
-social interaction (20)
-communication (9)
-alertness behavior (10)
-emotional behavior (9)

Independent Categories (43)
-sleep and rest (7)
-eating (9)
-home management (10)
-recreation and pastimes(8)
-work (9)

Short Form:

Somatic autonomy (17)
Mobility Control (12)
Psychic Autonomy and Communication (11)
Social Behavior (12)
Emotional Stability (6)
Mobility Range (10)

Administration Time: 20-30 minutes (Short Form-N/A)

Mode of Administration: Self and interview administered

Time Frame: General time

Scoring: Subjects check the items that represent them on a given day. Items are weighed so as to calculate an SIP percent score. Scores can be calculated for each of the categories as well as the two domains and an overall score.

Preference Based: No

Population Used In:

- in prostate cancer patients¹
- in head and neck cancer patients²
- in patients with advanced colorectal cancer³
- in patients with advanced prostate cancer⁴
- in older adults (65 to 95)⁵
- in patients with bladder cancer⁶
- in patients with colorectal liver metastasis patients⁷
- in patients with testicular cancer⁸
- in breast cancer patients⁹
- in breast cancer patients undergoing radiation therapy¹⁰
- in oral and pharyngeal cancer patients before and after surgery¹¹
- in patients undergoing chemotherapy for small cell lung cancer¹²

Reliability and Validity: (from McDowell et al.)

Reliability:

- Test-retest reliability was .88-.92 for the overall scores.
 - interview administered .97
 - self-administered .87
- Reproducibility for individual items averaged .50; for the 12 categories it was .82

- alpha coefficients were .94 for the overall version; alpha for the self-administered version was .81
- the short form version was as reliable as the full-length versions.

	<u>alpha coefficient</u>
Somatic autonomy	.78
Mobility Control	.85
Psych. Aut. and Com.	.77
Social Behavior	.81
Emotional Stability	.72
Mobility Range	.79

Validity:

- correlations of the SIP (a small sampling):
 - with a self-assessment of sickness .63
 - with a clinician's assessment of limitation .50
 - with a clinician's assessment of sickness .40
 - with an index of physical functioning .81
 - with KPS in rehabilitation patients .46
 - with KPS in nursing-home patients .42

Spanish version:

- test-retest correlations were .96 for the overall measure and ranged from .84 to .96 for the categories.
- correlations with:
 - self-perceived overall health .53
 - self-assessment of sickness .51

- self-assessment of dysfunction .63
- Index of Restricted Activity .54
- Index of Activities of Daily Living .45
- clinicians assessment of dysfunction .29
- speech therapists' assessment of speech pathology .23
- Reproducibility across:
 - illnesses .95-.98
 - types of administration .96-.98
 - interviewers .93-.99

Comments:

- “A repeated point of criticism concerning the SIP is its relatively large number of items. Deyo found that respondents experienced items not applying to their situation as redundant (De Bruin et al. 408).”
- Available in nine languages
- To learn more about this instrument go to: www.outcomes-trust.org

References:

- Badia X, Alonso J.** Validity and Reproducibility of the Spanish Version of the Sickness Impact Profile. *J Clin Epidemiol* 1996; 49(3):359-365.
- De Bruin AF, Diederiks JPM, De Witte LP, et al.** The Development of a Short Generic Version of the Sickness Impact Profile. *J Clin Epidemiol* 1994; 47(4): 407-418.
- McDowell I, Newell C.** The Sickness Impact Profile. In *Measuring Health: A Guide to Rating Scales* (2nd edition). New York: Oxford University Press. 1996, pp. 431-438.
- MedicalOutcomesTrust.** March 1996 Bulletin.
www.outcomes-trust.org/bulletin/0396bull.htm
- American Thoracic Society.** Quality of Life Resource: The Sickness Impact Profile.
www.atsol.org/sick.html

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- 1.Stockler MR; Osoba D; Corey P, et al. Convergent discriminative, and predictive validity of the Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) assessment and comparison with analogous scales from the EORTC QLQ-C30 and a trial- specific module. European Organisation for Research and Treatment of Cancer. Core Quality of Life Questionnaire. *J Clin Epidemiol* 1999 Jul;52(7):653-66.
 - 2.Hammerlid E; Persson LO; Sullivan M; Westin T. Quality-of-life effects of psychosocial intervention in patients with head and neck cancer. *Otolaryngol Head Neck Surg* 1999 Apr;120(4):507-16.
 - 3.Allen-Mersh TG; Glover C; Fordy C, et al. Relation between depression and circulating immune products in patients with advanced colorectal cancer. *J R Soc Med* 1998 Aug;91(8):408-13.
 - 4.Litwin MS; Shpall AI; Dorey F; Nguyen TH. Quality-of-life outcomes in long-term survivors of advanced prostate cancer. *Am J Clin Oncol* 1998 Aug;21(4):327-32.
 - 5.Andresen EM; Rothenberg BM; Panzer R, et al. Selecting a generic measure of health-related quality of life for use among older adults. A comparison of candidate instruments. *Eval Health Prof* 1998 Jun;21(2):244-64.
 - 6.Mansson A; Colleen S; Hermeren G; Johnson G. Which patients will benefit from psychosocial intervention after cystectomy for bladder cancer? *Br J Urol* 1997 Jul;80(1):50-7.

-
- 7.Earlam S; Glover C; Davies M, et al. Effect of regional and systemic fluorinated pyrimidine chemotherapy on quality of life in colorectal liver metastasis patients. *J Clin Oncol* 1997 May;15(5):2022-9.
 - 8.Fossa SD; Moynihan C; Serbouti S. Patients' and doctors' perception of long-term morbidity in patients with testicular cancer clinical stage I. A descriptive pilot study. *Support Care Cancer* 1996 Mar;4(2):118-28.
 - 9.Fallowfield LJ. Assessment of quality of life in breast cancer. *Acta Oncol* 1995;34(5):689-94.
 - 10.Graydon JE. Women with breast cancer: their quality of life following a course of radiation therapy. *J Adv Nurs* 1994 Apr;19(4):617-22.
 - 11.Langius A; Bjorvell H; Lind MG. Functional status and coping in patients with oral and pharyngeal cancer before and after surgery. *Head Neck* 1994 Nov-Dec;16(6):559-68.
 - 12.Bergman B; Sullivan M; Sorenson S. Quality of life during chemotherapy for small cell lung cancer. I. An evaluation with generic health measures. *Acta Oncol* 1991;30(8):947-57.

Spitzer Quality of Life Index (SQL-index)

Measure: SQL-index

Contact Person: WALTER O. SPITZER, M.D.

Potsdam Institute of Pharmacoeconomics
and Technology Assessment
McGill University
Otto-Erich-Strasse 7
14482 POTSDAM, GERMANY

telephone: +49.331.748.1986

Terms of Use: Contact the above.

General or Disease Specific: General for Cancer or Other Chronic Diseases

Number of Items: 5 items and a question at the end of the health professional administered instrument that asks the interviewer how comfortable they are that the scoring of the items will be accurate.

Domains: Overall Well-Being
-Activity
-Daily Living
-Health State
-Support From Others
-Outlook on Life

Administration Time: Median completion time of 1 minute (given by clinician)

Mode of Administration: There is both a version administered by a health professional and a version for self-administration.

Time Frame: "During the last week."

Scoring: Scores of 0,1, or 2 are possible for each category for a total score of 0 to 10 for the index. Higher scores indicate higher QoL.

Preference Based: No.

Population Used In:

- in patients with advanced cancer¹
- after surgical treatment of gastric carcinoma²
- in patients with recurrent head and neck cancer³
- in patients with advanced cancer⁴
- in patients with lung cancer⁵
- in patients with ovarian cancer⁶
- in patients with metastatic malignant melanoma⁷
- in patients undergoing testis cancer therapy⁸
- with severe mental disorders⁹

Reliability and Validity:

Reliability:

From Spitzer, et al.

-Internal Consistency Overall: $\alpha = .775$.

From McDowell & Newell:

-Item-total correlations ranged from .49 (activity) to .86 (outlook)

-Inter-rater reliability- samples Spearman correlations ranged from .74-.84

Validity:

From McDowell & Newell

-The Spitzer QoL Index has been compared to the Karnofsky Performance Status Scale in several studies yielding correlations of .41, .72, and .83.

-Studies have also been done with the Barthel Index (.52), the Functional Independence Measure (.45), and with the Katz Index of ADL (.48).

-Index scores had a .42 correlation with a Breast Cancer Questionnaire.

-A .53 Kendall rank correlation was found between the Index scores and a visual analogue scales.

-Individual items on the Spitzer have been compared to other scales.

Comments:

-More than 59% of doctors who participated in the original validation study reported being "absolutely confident" or "very confident" in their scores while 36% were "quite confident."

-The measure does not discriminate amongst well people.

-More suited to the global assessment of seriously ill patients long-term rather than short-term usage.

References:

Spitzer WO, Dobson AS, Hall J, et al. Measuring the Quality of Life of Cancer Patients: A concise QL-index for Use by Physicians. *Journal of Chronic Diseases* 1981; 34: 585-597.

McDowell S, Newell C. The Quality of Life Index. In: *Measuring Health: A Guide to Rating Scales and Questionnaires*. New York: Oxford University Press, 1996:405-409.

¹ **Sloan JA, Loprinzi CL, Kuross SA, et al.** Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998 Nov;16(11):3662-73.

² **Zieren HU, Zippel K, Zieren J, Muller JM.** Quality of life after surgical treatment of gastric carcinoma. *Eur J Surg* 1998 Feb;164(2):119-25.

³ **Robert F, Soong SJ, Wheeler RH.** A phase II study of topotecan in patients with recurrent head and neck cancer. Identification of an active new agent. *Am J Clin Oncol* 1997 Jun;20(3):298-302

⁴ **Perez DJ, McGee R, Campbell AV, et al.** A comparison of time trade-off and quality of life measures in patients with advanced cancer. *Qual Life Res* 1997 Mar;6(2):133-8.

⁵ **Abratt R, Viljoen G.** Assessment of quality of life by clinicians--experience of a practical method in lung cancer patients. *S Afr Med J* 1995 Sep;85(9):896-8.

⁶ **Guidozzi F.** Living with ovarian cancer. *Gynecol Oncol* 1993 Aug;50(2):202-7.

⁷ **Coates A, Thomson D, McLeod GR, et al.** prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. *Eur J Cancer* 1993;29A(12):1731-4.

⁸ **Tamburini M, Filiberti A, Barbieri A, et al.** Psychological aspects of testis cancer therapy: a prospective study. *J Urol* 1989 Dec;142(6):1487-9; discussion 1490.

⁹ **Sainfort F, Becker M, Diamond R.** Judgments of quality of life of individuals with severe mental disorders: Patient self-report versus provider perspectives. *Am J Psychiatry* 1996 Apr;153(4):497-502.

Satisfaction with Decision Scale

Measure: SWD

Contact Person: Dr. Margaret Holmes-Rovner
Department of Medicine
B220 Life Sciences Building
Michigan State University
East Lansing, Michigan 48824-1317
Phone: (517) 353-3128
Email: mholmes@msu.edu

Terms of Use: N/A

General or Disease Specific: Decision General

Number of Items: 6

Domain: Decisional confidence

Administration Time: No data given though should take 2-3 minutes.

Mode of Administration: self-administered (though other forms of administration may be acceptable)

Time Frame: general (no specific time frame)

Scoring: each item has a 1-5 scale with 1 representing "strongly disagree" (not confident in the decision) and 5 representing "strongly agree" (quite confident in the decision.)

Preference Based: No.

Population Used In: N/A

Reliability and Validity:

Reliability:

-Cronbach's alpha was .86.

Validity:

Intercorrelations among variables

	Satisfaction with Decision
Decisional Conflict	-.54
Restrictions	-.27
Satisfaction with Provider	.23
Desire to Participate	-.18
Confidence in Decision	.64
Knowledge	.21
Perceived Knowledge	.48
Education	.22

Income	.12
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-Factor loading of two scales (Decisional Conflict and Restricted Decision) and the Satisfaction with Decision were carried out. "In summary, the internal consistency of each of these three scales, the observed correlation between the scales, and their intercorrelations corrected for attenuation due to unreliability indicate that the scales measure discriminable constructs, although the SWD scale is clearly related to the Decisional Conflict scale (Holmes-Rovner et al.)"

Comments:

- in a Medline search, no other articles were found containing the SWD.
- a half standard deviation is suggested to reflect a change in satisfaction with decision when using the SWD scale score.
- written at an eighth-grade level
- originally developed to assist women with making a decision regarding whether or not to engage in Hormone Replacement Therapy (HRT).

References:

Holmes-Rovner M, Kroll J, Schmitt N, et al. Patient satisfaction with health care decisions: The Satisfaction with Decision Scale. *Med Decis Making* 1996; 16: 58-64.

Summary of Work Completed-Summer 1999 Jill M. Paulson (Jill_Paulson@brown.edu)

Completed Measures:

- Breast Cancer Chemotherapy Questionnaire (BCCQ)
- Brief Symptom Inventory (BSI)
- Cancer Rehabilitation Evaluation System (CARES)
- Cancer Rehabilitation Evaluation System-Short Form (CARES-SF)
- Center for Epidemiologic Studies Depression Scale (CESDS)
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Item (QLQ-C30)
- Functional Assessment of Chronic Illness Scales (FACIT)
- Functional Living Index-Cancer (FLIC)
- Health Utilities Index (HUI) *
- Hospital Anxiety and Depression Scale (HADS)
- Impact of Event Scale (IES) **
- Karnofsky Performance Status Scale (KPS)
- Medical Outcomes Study 12-Item Short Form (SF-12) Health Survey (SF-12)
- Medical Outcomes Study 36-Item Short Form (SF-36) Health Survey
- Memorial Symptom Assessment Scale (MSAS)
- Mental Health Inventory (MHI) ***
- Profile of Mood States and Short Form (POMS)
- Quality of Well-Being Scale (QWB)
- Rotterdam Symptom Checklist
- Satisfaction with Decision Scale (SWD)
- Sickness Impact Profile (SIP)
- Spitzer Quality of Life Index (SQL Index)
- Symptom Checklist 90-Revised (Formerly the Hopkins Symptom Checklist 90) ****
- Symptom Distress Scale (SDS)
- Quality-Adjusted Time Without Symptoms of disease and Toxicity of treatment (Q-TWiST)

*- Two ILL articles are still on order. Many fields have not been completed.

** - See IES folder with attached email for new contact and instrument information

*** - The MHI has not yet been completed. Not enough information has been gathered.

**** - Information is being sent regarding reliability and validity and other pertinent information.

	Copies of the Measure?
BCCQ	
BSI	
CARES	
CARES-SF	
CESDS	
QLQ-C30	
FACIT	
FLIC	
HADS	
HUI	
IES	
KPS	
MHI	

MSAS	
POMS	
SF-12	
SF-36	
QWB	
Rotterdam	
SWD	
SIP	
SCL-90-R	
SQL Index	
SDS	
Q-TWiST	

Interlibrary loan orders:

No.	DDS#	Title	Status	Date	Fee
1.	(23483)	reliability of the Health Utilities Payment Method: RX4395836	Sent/ILL	07/16/99	\$ 0.00
2.	(23482)	psychometric properties of the Healt Payment Method: RX4395836	Sent/ILL	07/16/99	\$ 0.00
3.	(23466)	Clinical Utility of the impact of Payment Method: RX4395836	Completed	07/26/99	\$ 12.00
4.	(23450)	the structure of psychological dist Payment Method: RX4395836	Completed	07/20/99	\$ 12.00
5.	(23419)	Spanish version of the Rotterdam Sy Payment Method: RX4395836	Completed	07/16/99	\$ 12.00

Measures that are possibilities to add to the library:

- Global Self-Assessment
- Long Term Quality of Life
- Life Satisfaction Questionnaire (LSQ-32)
- Perceived Adjustment to Chronic Illness (PACIS)
- Easter Cooperative Oncology Group (ECOG) Performance Status Rating (PSR)
- The Quality-Quantity Questionnaire (Q-Q Questionnaire)
- Quality of Life Scale-Cancer 2 (QOL-CA)
- Perceived Susceptibility to Breast Cancer and Perceived Benefits From Breast Self-Exam
- General Well-Being Index (There is a folder in the file drawer of articles that I started gathering)

Other:

- AL Potsky abstracts are in the green folder marked "Misc...QoL library." His instrument could not be found.
- The NCI grant search that I did for Jeanne is labeled "#2-QoL" in the Reference Manager.
- A backup copy of all files including the #2-QoL library is on the zip disk.
- Rhonda is the middle of putting references from the library in Reference Manager.
- All completed measures that have put in Reference Manager are in the pink folder.
- I went over Jeanne's comments on the first batch. If something was not included in the reliability and validity section, it probably was not in any article. Specifically, the CARES has no Cronbach Alphas because I only have the CIPS (the previous CARES) data (see Shag, et al. 1990).

List of Journals

ACP Journal Club
American Economic Review
American Journal of Epidemiology
American Journal of Managed Care
American Journal of Public Health
American Journal of Public Health
Annals of Internal Medicine

Business and Health

Cancer
Cancer Epidemiology Biomarkers and Prevention
Cancer Investigation
Cancer Research

Epidemiologic Reviews

Gerontologist

Health Affairs
Health and Health Care of the Medical Population
Health Care Financial Management
Health Care Financing Review
Health Grants and Contracts Weekly
Health Service Research
Hospitals

Inquiry

JAMA
Journal of American Board of Family Practice
Journal of American Health Policy
Journal of Clinical Epidemiology
Journal of Economic Literature
Journal of Economic Perspectives
Journal of Evaluation in Clinical Practice
Journal of General Internal Medicine
Journal of Gerontology
Journal of Health Economics
Journal of Health Politics, Policy and Law
Journal of Human Resources
Journal of Medical Education
Journal of the American Board of Family Practice
Journal of the National Cancer Institute

Journal of the National Cancer Institute Monograph
Journal of Outcomes Measurement
Journal of Political Economy

Medical and Health Perspectives
Medical Care
Medical Care Research and Review
Medical Decision Making
Medical Group Management
Medicare and Medicaid Guide
Medicine and Health (Faulkner and Gray)
Milbank Memorial Fund Quarterly/Health and Society
Milbank Quarterly
Modern Health Care
Monographs (Journal of the National Cancer Institute)
Monthly Labor Review

National Journal
New England Journal of Medicine

Oncologist
Oncology
Oncology Nursing Forum
Operations Research

Papillomavirus Report
Public Health Report

Quality of Life Research
Quality Management in Health Care (QMHC)

Science
SCLD
Social Science and Medicine
Social Security Bulletin
Socioeconomic Characteristics of Medical Practice
S-Plus

The NBER Digest

USPSTF-Preventive Services Task Force

Vital and Health Statistics